The role of immunotherapy in in vitro fertilization: a guideline

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Adjuvant immunotherapy treatments in in vitro fertilization (IVF) aim to improve the outcome of assisted reproductive technology (ART) in both the general ART population as well as subgroups such as patients with recurrent miscarriage or implantation failure. The purpose of this guideline is to evaluate the role of immunomodulating therapy in ART. Unfortunately, many of the evaluated therapies lack robust evidence from well-designed adequately powered randomized controlled trials to support their use. Immunotherapies reviewed in the present document are either not associated with improved live-birth outcome in IVF or have been insufficiently studied to make definitive recommendations. (Fertil Steril® 2018;110:387–400. ©2018 by American Society for Reproductive Medicine.)

Successful outcomes in assisted reproductive technology (ART) cycles depend on the developmental competence of transferred embryo(s) and endometrial receptivity. Multiple factors are believed to be involved in endometrial receptivity, including the hormonal preparation of the endometrium, contractility of the myometrium, and the interaction between the embryo and endometrium, the latter of which inherently involves immunological mechanisms. In an effort to improve outcomes in ART cycles in general, and in patients with recurrent implantation failure and/or pregnancy loss, aduvant immunotherapies have been introduced into in vitro fertilization (IVF) treatment cycles. The rationale behind the use of these therapies is that they may correct an immunological imbalance resulting in improved and sustained implantation of the developing embryo, ultimately leading to improved live-birth outcome. While some of these medications (e.g., aspirin and corticosteroids) have been used for many years and are relatively low cost, others (e.g.,

intravenous fat emulsions and granulocyte colony–stimulating factor [G-CSF]) are newer, of higher cost, and with risks that have been poorly characterized. It is imperative that physicians providing ART treatments have a full understanding of the potential risks and benefits associated with adjuvant immunotherapy in order to appropriately counsel patients regarding their use. In the absence of well-designed adequately powered randomized controlled trials (RCTs), or other methodologically rigorous quantitative assessment design studies, patients must be informed of uncertain benefits and risks (1). In some investigations, adjuvant immunotherapies have been administered based on the results of immunological testing. Given the lack of a clear relationship between immunophenotypes and ART outcomes, the use of immunological testing in the general ART population cannot be recommended (2, 3). The present guideline is based on a systematic review of the literature regarding immunotherapy in IVF with the goal of informing the practitioner

about how to provide evidence-based care.

LIMITATIONS OF THE LITERATURE

Multiple challenges exist in interpreting the literature related to immunotherapy and IVF outcomes, which includes few well-designed randomized studies. Many of the cited investigations are more than 20 years old, and their applicability to modern ART is uncertain. Additionally, many of the investigations are underpowered and/or address surrogate outcomes such as embryo development and clinical pregnancy rate rather than live birth. Multiple investigations also include combined treatment regimens rather than single-component treatments, so it is difficult to attribute any change in outcome to a given treatment. Some of the investigated therapies (e.g., aspirin) may have multiple mechanisms of action, such that an observed effect may or may not be due to an immunological mechanism. Finally, many of the cited studies include narrowly defined populations based on immunological testing which may not be readily available and/or reproducible.

METHODS

This clinical practice guideline was based on a systematic review of the literature performed in the electronic

database MEDLINE through PubMed on August 17, 2017. No limit or filter was used for the time period covered or English language, but articles were subsequently culled for English language. This electronic search and examination of reference lists from primary and review articles yielded 1,525 studies, of which 96 studies were included.

A combination of the following medical subject headings or text words were used: abdominal pain/chemically induced; acetylsalicylic acid; adalimumab; adjuvants, immunologic; adrenocorticotropic hormone; adverse; adrenal cortex hormones; allogenic leukocyte immunization; alloimmunization; antibodies, anticardiolipin; antibodies, antinuclear; antibodies, antiphospholipid; anti-cardiolipin antibody; antigens; anti-nuclear antibodies; anti-nuclear antibody; antinuclear antibodies; antinuclear antibody; antiphospholipid antibody; antiphospholipid antibodies; antithyroid antibody; antithyroid antibodies; aspirin; assisted reproduction; autoantibodies; corticosteroid/s; corticotropin-releasing hormone; cost; cytokine; cytokines; dexamethasone; drug costs; embryo implantation; embryo transfer; Enbrel; estrogen/s; etanercept; fertility agents, female/adverse effects; fertilization in vitro/methods; filgrastim; G-CSF; glucocorticoid/s; GM-CSF; granulocyte colony-stimulating factor; harm; HLA; HLA antigens; human leukocyte antigen; Humira; ICSI; IL-10; IL-17; IL-27; immune modulatory; immune therapy; immunoglobulins, intravenous; immunoglobulins/therapeutic use; immunologic tests; immunomodulation; immunomodulatory; immunosuppression; immunotherapy; in vitro fertilisation; in vitro fertilization; interleukin-10; interleukin-17; interleukin-27; intracytoplasmic sperm injection; intralipid; intralipid infusion; intrauterine insemination; intravenous immunoglobulin; intravenous immunoglobulins, human; intravenous lipids; irritable bowel syndrome/chemically induced; IVF; IUI; killer cells, natural; leukocyte antibodies; leukocyte antibody; lupus anticoagulant; lupus coagulation inhibitor; methylprednisolone; natural killer cells; nausea/chemically induced; ovulation induction; prednisone; progesterone; regulatory T cells; risk; safety; sperm injections, intracytoplasmic; steroid/s; T cells; T regulatory cells; tacrolimus; Th1; Th1 cells; Th2; Th2 cells; thyroid peroxidase antibodies; thyroid peroxidase antibody; TNF; transforming growth factor beta; Treg cells; tumor necrosis factor; tumour necrosis factor; tumor necrosis factor-alpha; vomiting/chemically induced.

Initially, titles and abstracts of potentially relevant articles were screened and reviewed to develop inclusion/exclusion criteria. Only studies that met the inclusion criteria were assessed in the final analysis. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with an outcome measure (pregnancy, ovulation, or live-birth rates); meta-analyses; and relevant articles from bibliographies of identified articles (Table 1).

Four members of an independent task force reviewed the full articles of all citations that potentially matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and resolved by consensus or arbitration after consultation with an independent reviewer/epidemiologist.

TABLE 1

Summary of inclusion/exclusion criteria.

Include	Exclude
Level I and II studies, systematic reviews, meta-analyses	Level III studies: series, case reports, reviews, opinions, off topic
Human studies	Animal studies
English	Non-English
Studies with a comparison group	Studies without a comparison group
Studies with a primary focus on IVF	Non-IVF fertility treatment
Aspirin as monotherapy for IVF outcomes	Agents that are both immunomodulating and have other progestational effects
Corticosteroids during ovarian stimulation	Anticardiolipin studies that focus on recurrent pregnancy loss
Peri-implantation corticosteroids	Anticoagulants
G-CSF and GM-CSF and embryo development, aneuploidy, endometrial thickness, or IVF outcomes	Antithyroid antibodies
Intravenous fat emulsions and IVF outcomes	DHEA
IVIG and IVF outcomes	IUI
Adalimumab and IVF outcomes	Metformin
Peripheral mononuclear cells and IVF outcomes	OHSS
Seminal plasma and IVF outcomes	PCOS
Antibody-free preparation of spermatozoa and IVF outcomes	Thyroid
Tacrolimus and IVF outcomes	Vasodilators
	Uterine relaxants
	Patients on immunomodulation therapy for known autoimmune conditions (e.g., rheumatoid arthritis)
	Progesterone (with mixed hormonal and immunological properties)
	Hypertensive complications
	Aspirin in combination with other therapies

Note: DHEA = dehydroepiandrosterone; G-CSF = granulocyte colony–stimulating factor; GM-CSF = granulocyte/macrophage colony–stimulating factor; IUI = intrauterine insemination; IVIG = intravenous immunoglobulin; IVF = in vitro fertilization; OHSS = ovarian hyperstimulation syndrome; PCOS = polycystic ovary syndrome.

ASRM. Immunotherapy and IVF. Fertil Steril 2018.

Level of Evidence

The level of the evidence was evaluated using the following grading system and is assigned for each reference in the bibliography:

Level I

- Systematic review of randomized controlled trials (RCTs)
- RCTs

Level II

- Systematic review of a combination of RCTs, controlled trials without randomization, and cohort studies
- Controlled trials without randomization
- Cohort studies
- Case-control studies

Level III

- Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions based on clinical experience, and reports of expert committees

Quality of Evidence

The quality of the evidence was evaluated using the following grading system, adapted from the Johns Hopkins Nursing Evidence-based Practice grading system, and is assigned for each reference in the bibliography:

A: High Quality

- Consistent, generalizable results; sufficient sample size for the study design; adequate control; definitive conclusions; consistent recommendations based on a comprehensive literature review that includes thorough reference to scientific evidence

B: Good Quality

- Reasonably consistent results; sufficient sample size for the study design; some control; fairly definitive conclusions; reasonably consistent recommendations based on a fairly comprehensive literature review that includes some reference to scientific evidence

C: Low Quality or Major Flaws

- Little evidence with inconsistent results; insufficient sample size for the study design; conclusions cannot be drawn

Strength of Recommendations

The entirety of the literature was then used to develop recommendations based on the quality of the literature. The strength of the recommendation was evaluated as follows:

Grade A: There is good evidence to support the recommendations, either for or against.

(From consistent Level-I studies of High quality [Grade A])

Grade B: There is fair evidence to support the recommendations, either for or against. (From principally Level-II studies of Good quality [Grade B])

Grade C: There is insufficient evidence to support the recommendations, either for or against. (From Level-II studies of Low quality [Grade C], or when there are conflicting data from studies of Good quality)

Aspirin

Aspirin has been investigated as a means to increase blood flow to the ovaries and thereby improve oocyte yield and/or quality, and increase blood flow to the uterus which may improve endometrial thickness and receptivity (4, 5). With theoretical mechanisms of action that could involve both anti-inflammatory and anti-platelet activity, aspirin has been investigated as an attractive potential adjuvant to IVF.

Five RCTs investigating the use of aspirin in ART reported outcomes for implantation rate. Four of these did not show a benefit of aspirin for implantation rate in IVF (6–9), while the remaining trial (n=149, aspirin group) did show a significantly improved implantation rate with aspirin use (10). A retrospective cohort study also failed to demonstrate a benefit of aspirin for implantation rate, and found a statistically significantly higher fertilization rate in the nonaspirin group (54.7% aspirin vs. 58.2% no aspirin, respectively, $P < .01$) (11).

Nine RCTs reported an association between aspirin and pregnancy rate in IVF; pregnancy rate was variably defined. Several studies defined clinical pregnancy as presence of a gestational sac (6, 12) or fetal cardiac activity (6,8–10,13), while the remaining studies did not specify how pregnancy was defined (14–16). While a single RCT of 298 patients undergoing IVF for tubal factor infertility showed a significantly improved pregnancy rate among women who received low-dose aspirin (45% vs. 28%, $P < .05$) (10), eight RCTs showed no benefit of aspirin use for pregnancy rate in ART (6,8,9,12–16). There was no benefit of aspirin for pregnancy rate in three cohort studies (11, 17, 18), while two cohort studies showed a higher pregnancy rate with aspirin use (19, 20).

Multiple RCTs have failed to demonstrate a benefit of aspirin for live-birth rate (13, 14, 16, 21) or ongoing pregnancy rate (7) in ART, and there are no RCTs that have shown an improved live-birth rate. There are three retrospective analyses demonstrating an association with aspirin and higher live-birth rate: 74.8% aspirin vs. 63.7% controls, $P < .05$; 27.2% aspirin vs. 23.2% controls (odds ratio [OR] 1.2; confidence interval [CI] 1.0–1.6); and adjusted OR 1.48, CI 1.08–2.02, respectively (19, 20, 22). However, two other retrospective analyses published around the same time failed to show an association with live-birth rate and aspirin use (11, 18). Another more recent study showed no benefit for ongoing pregnancy rate with aspirin (17).

A meta-analysis of six RCTs comparing aspirin to placebo or no treatment during IVF/intracytoplasmic sperm injection (ICSI) found no beneficial effect on pregnancy (risk ratio [RR] 1.09; 95% CI 0.92–1.29), live-birth rate per cycle (RR 0.87; 95% CI 0.57–1.34), or live-birth rate per embryo transfer (ET) (RR 1.08; 95% CI 0.83–1.40) [23]. Similarly, another meta-analysis published the same year included seven trials of participants undergoing controlled ovarian stimulation (COS), IVF, or ICSI, and found no benefit of aspirin compared to placebo or no treatment for clinical pregnancy rate (RR 1.11; 95% CI 0.95–1.31) or live-birth rate (RR 0.94; 95% CI 0.64–1.39), although this study lacked power when studies were pooled [24]. In contrast, a meta-analysis of 10 RCTs, including a reanalysis of a prior meta-analysis [23], showed that aspirin may increase clinical pregnancy rates (fixed effects RR 1.15; 95% CI 1.03–1.27), although there was a large variation in results among included studies [25]. A meta-analysis of 10 RCTs published a few years later found no improvement in clinical pregnancy rate (pooled OR 0.86; 95% CI 0.69–1.1) or ongoing pregnancy rate (pooled OR 0.85; 95% CI 0.65–1.1) [26]. A more recent meta-analysis of 17 RCTs comparing aspirin with no aspirin or placebo in IVF/ICSI couples showed a higher pregnancy rate (OR 1.19; 95% CI 1.01–1.39) but did not show a benefit for live-birth rate (OR 1.08; 95% CI 0.90–1.29) [27]. Most recently, a Cochrane systematic review of 13 low- to moderate-quality trials of subfertile women undergoing ART showed no benefit of aspirin in IVF for pregnancy (RR 1.03; 95% CI 0.91–1.17; 10 trials) or live-birth rates (RR 0.91; 95% CI 0.72–1.15; 3 trials) [28].

Aspirin monotherapy has also been investigated for use in specific populations undergoing IVF. Among recipients of oocyte donation, low-dose aspirin improved implantation rate but not live-birth rate in patients with a thin endometrium [16].

While aspirin is an inexpensive therapy with little overall risk, studies do not demonstrate that it improves the success of IVF. Therefore, its use is not recommended for use in the general IVF population. (See Supplemental Table 1, listing aspirin dosing and/or timing and IVF outcomes.)

Summary Statements

- Given the lack of evidence to support improved IVF outcomes, there is 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. (From Level-I studies of Good and High quality). (Grade A).

Corticosteroids

During ovarian stimulation. Corticosteroids are steroid hormones produced in the adrenal cortex in response to adrenocorticotropic hormone from the anterior pituitary. Synthetic forms (dexamethasone, hydrocortisone, prednisolone, methylprednisolone, and 16-methyl prednisolone) have been investigated for their potential ability to improve ovarian response to COS, to reduce the amount of exogenous gonadotropins required, and to optimize the intrauterine environ-

ment to increase the likelihood of implantation after IVF. In addition, corticosteroids have been hypothesized to improve the outcome of IVF with conventional insemination in cases where the male partner has sperm autoantibodies.

The rationale for using corticosteroids to improve ovarian response to COS is based on several possible mechanisms by which corticosteroids can affect ovarian function. Dexamethasone may directly mediate proper folliculogenesis, as it acts as a substrate for the enzyme 11-beta-hydroxysteroid dehydrogenase type I which is found in luteinized granulosa cells and oocytes [29, 30]. Corticosteroids can suppress elevated androgen levels, type I which are considered detrimental to normal folliculogenesis, by acting on the ovaries, adrenals, and pituitary glands. Furthermore, these agents could sensitize the ovaries to the actions of exogenous gonadotropins by increasing production of growth factors such as insulin-like growth factor (IGF)-1. A significant rise in follicular cortisol has been observed prior to ovulation, suggesting that corticosteroids may play an important role in oocyte maturation and ovulation [31–33].

Despite differing study designs and inclusion criteria, several Level-I studies [34–37] have refuted the hypothesis that the administration of corticosteroids during COS leads to an improvement in ovarian response or clinical outcomes. A trial randomized 78 normo-ovulatory women with tubal factor infertility to receive 0.5 mg or 1 mg of dexamethasone during COS vs. no treatment [34]. This trial demonstrated no improvement in implantation rate (controls 13%, dexamethasone 0.5 mg 11%, and dexamethasone 1 mg 12%) or pregnancy rate (controls 20%, dexamethasone 0.5 mg 16.5%, and dexamethasone 1 mg 20.8%) [34]. Another trial randomized 42 patients with unexplained or anovulatory infertility and a history of poor response in at least two prior IVF cycles to 0.5 mg dexamethasone during COS or no treatment, but found no benefit of treatment with low-dose dexamethasone in the studied population of low responders [36]. A third RCT also demonstrated no improvement in implantation (8.1% treatment vs. 7.8% controls) or pregnancy rate (13.5% treatment vs. 12.8% controls) [35]. A later trial randomized 313 patients under age 39 years to either 10 mg daily oral prednisolone or no treatment for 4 weeks, starting on the first day of ovarian stimulation [37]. There was no difference in ongoing pregnancy or deliveries between the treatment groups (prednisolone 39.6% vs. controls 37.1%). The results of these trials were consistent in demonstrating that treatment with corticosteroids during COS did not significantly affect the number of developing follicles [36], oocyte yield, fertilization, or clinical pregnancy rate [34, 36, 37]. These trials were limited by their lack of a placebo and failure to provide a power analysis to demonstrate an adequate sample size to evaluate the hypothesis that corticosteroids improve ovarian response to COS. A more recent two-center, double-blinded RCT randomized 290 patients to 1 mg dexamethasone or placebo and found a reduced rate of cycle cancellation for poor response in the treatment group (2.8%) vs. controls (12.4%, $P < .002$) [29]. However, there were no significant differences in fertilization, implantation, or clinical pregnancy rate per cycle start. Another RCT included 395 first-time IVF patients with normal ovarian reserve who were treated daily with

low-dose aspirin (100 mg) combined with prednisone (10 mg/day from the beginning of ovarian stimulation to ET, 30 mg/day for 5 days starting from the day of transfer, and 10 mg/d thereafter, until the day of pregnancy test) (15). Patients in the treatment group were compared with control patients who did not receive a placebo. The treatment group had significantly improved ovarian response, with higher estradiol levels on the day of human chorionic gonadotropin (hCG) trigger (2,082 ± 741 vs. 1,728 ± 672, $P<.001$) and significantly more oocytes retrieved (14.0 ± 6.5 vs. 10.5 ± 5.1, $P<.001$) (15). Despite these outcomes, fertilization, implantation, clinical pregnancy, and early pregnancy loss rates were similar. A meta-analysis also did not identify a difference in pregnancy rate, clinical pregnancy rate, or implantation rate in women undergoing IVF/ICSI and treated with prednisolone vs. controls (pregnancy rate: RR 1.02, 95% CI 0.84–1.24; clinical pregnancy rate: RR 1.01, 95% CI 0.82–1.24; implantation rate: RR 1.04, 95% CI 0.85–1.28) (38).

There are two RCTs that contradict these findings and report on corticosteroids positively impacting pregnancy rates in patients undergoing ovarian stimulation (39, 40). One of these trials randomized 146 hyperandrogenemic, infertile patients undergoing COS with exogenous gonadotropins and/or clomiphene citrate to receive 7.5 mg of oral prednisolone daily from cycle day 1 until pregnancy or menstrual bleeding or no treatment (39). Treatment suppressed serum dehydroepiandrosterone sulfate (DHEA-S) and testosterone and led to improved follicular response, signified by significantly higher estradiol levels on the day of hCG trigger and clinical pregnancy rate (prednisolone group 21.9% vs. no prednisolone 8.2%, $P=.037$) (39). Another RCT included patients (N=129; n=64 received treatment) with endometriosis and/or tubal factor infertility who received daily prednisolone (10 mg from cycle day 3, increased to 60 mg from oocyte retrieval to ET) (40). Corticosteroid treatment significantly improved the pregnancy rate in patients with endometriosis and tubal factor infertility, whereas treatment did not have a benefit in the patients with tubal factor alone (40). In the subset of patients who tested positive for autoantibodies (antinuclear antibodies [ANA], lupus anticoagulant, anticardiolipin antibody and/or rheumatoid factor), those who received corticosteroids had a significantly higher pregnancy rate (40.9% vs. 14.8%, $P<.05$) (40). However, the comparison of these subgroups may have been confounded by differences in baseline characteristics as randomization was not performed according to autoantibody status. The results of these RCTs should be interpreted with caution as they are limited by a lack of a power analysis, significant sources of heterogeneity in the treatment protocol (such as the number of embryos transferred), and limited generalizability to today's IVF treatment paradigm, as they were published over 20 years ago. The most recent study, a meta-analysis published in 2017, included four RCTs (involving a total of 416 couples with various infertility diagnoses) which demonstrated that daily corticosteroids (10 mg prednisolone or 0.5 mg dexamethasone during ovarian stimulation up until oocyte retrieval) did not impact clinical pregnancy or live-birth rate (31).

While several retrospective, observational studies have reported that corticosteroid treatment may improve IVF success rates, these studies are limited by significant methodologic flaws (41–46). (See Supplemental Table 2, listing the use of corticosteroids and IVF outcomes and study limitations.)

Peri-implantation corticosteroids. Uterine receptivity is regulated by locally acting growth factors and cytokines (47–50) that have important roles in mediating immunological and non-immunological activity within the endometrium. Natural killer (NK) cells play an important role in maintaining maternal-fetal immune tolerance and regulating trophoblast invasion (38). Aberrant cytokine activity and overactivity of NK cells have been associated with implantation failure and early pregnancy loss (47, 51–53). The administration of corticosteroids around the time of implantation has been proposed as a strategy to normalize NK cell activity and cytokine expression, and suppress inflammatory mediators to improve endometrial receptivity and the odds of successful implantation (47, 54, 55).

Several RCTs have failed to demonstrate any effect of peri-implantation corticosteroids on ET outcome (35, 47, 56, 57). An RCT which randomized 99 normo-ovulatory women with tubal factor infertility to 0.5 mg dexamethasone for 5 days from time of ovulation to ET, reported a lack of improvement in implantation, clinical pregnancy, or live-birth rates (35). Similarly, there was no difference ($P>.05$) in implantation (16% vs. 11%), clinical pregnancy (43.5% vs. 32.3%), or ongoing pregnancy rate (30.7% vs. 28%) in a trial of 75 IVF patients randomized to receive either 60 mg prednisone daily for 4 days from time of oocyte retrieval, or placebo, respectively (57). Both of these trials lacked power analyses to demonstrate an adequate sample size to detect a meaningful effect on clinical outcome. A larger study of 206 patients randomized to receive either methylprednisone or placebo at the time of oocyte retrieval in fresh transfer cycles or a day prior to embryo thaw in frozen ET cycles, reported no difference in implantation or clinical pregnancy rate in either group (56). A lack of effect of peri-implantation corticosteroid administration on clinical outcome was reiterated by a recent, large, systematic review which included 14 RCTs involving 1,879 patients who received either corticosteroids or no treatment prior to transfer (47) as well as a prospective cohort study (58).

The only studies to report that peri-implantation corticosteroid treatment improved ET outcome involved patients with serum autoantibodies. Autoimmune thyroid disorders are characterized by the presence of antithyroid antibodies, such as antithyroid peroxidase and/or thyroglobulin. Thyroid autoimmunity has been associated with recurrent pregnancy loss, preterm birth, and recurrent IVF failure (59). A single study randomized patients with anti-thyroglobulin and thyroid peroxidase antibodies (n=60; age ≤ 38 years) to receive either 5 mg prednisolone daily from day of oocyte retrieval to pregnancy test or no treatment (59). The treatment group had higher clinical pregnancy and live-birth rates compared with the control group (clinical pregnancy: 46.6% vs. 16.6%, $P=.03$; live birth: 46.6% vs. 20%, $P=.055$) (59).

A retrospective cohort study of 120 women positive for serum ANA reported that patients who received prednisolone (in a dose ranging from 15 to 60 mg per day, starting the day after oocyte retrieval) had significantly higher implantation and clinical pregnancy rates than ANA-positive women who did not receive corticosteroids (60). However, there was no significant difference in live-birth rate. This study may have been underpowered to analyze the effect of the intervention on live-birth rate. The results should be interpreted with caution as this was a retrospective, nonrandomized study involving a non-uniform intervention, with the corticosteroid dose being adjusted according to patient tolerance of side effects (60). Several other retrospective cohort studies have demonstrated corticosteroid treatment to have a positive clinical impact in autoantibody-positive subjects (43–46). However, all these studies were confounded by the fact that treated subjects underwent co-administration of corticosteroids with aspirin. Two small cohort studies suggested that glucocorticoid treatment was associated with improved pregnancy rates in the setting of assisted hatching (61) and tubal factor infertility (62). However, both investigations were limited by small sample size, no live-birth outcome, and inappropriate statistical analyses (considering repeat cycles as independent observations).

The only Level-I study to assess the efficacy of corticosteroids for autoimmune-mediated male infertility reported that randomization of men with antisperm antibodies to 20 mg of prednisolone daily for 2 weeks prior to IVF vs. no treatment did not reduce the amount of sperm-bound antibody and did not improve IVF outcome (63). Of note, this study was underpowered and did not account for female factor infertility.

Summary Statements

- There is good evidence to recommend against the routine use of corticosteroids during stimulation to improve the outcome of live birth in ART cycles in the general population. (From principally Level-I studies of Good quality). (Grade A).
- There is good evidence to recommend against the routine use of corticosteroids during the implantation window to improve the outcome of live birth in ART cycles in the general population. (From principally Level-I studies of Good quality). (Grade A).
- Additional studies are needed to determine if there are any subpopulations where benefit may exist but are not proven.

Granulocyte Colony–stimulating Factor (G-CSF) and Granulocyte/Macrophage Colony–stimulating Factor (GM-CSF)

Discovery of granulocyte/macrophage colony-stimulating factor (GM-CSF) and G-CSF production and receptors in reproductive tissues and impaired fertility of model animals with introduced mutations in these cytokines raised hope that supplementation of embryo cultures could improve IVF outcomes (64). Several aspects were investigated in this guideline: 1) improvement of embryo development or lowering of the aneuploidy rate, 2) improvement in endometrial thickness, and 3) overall IVF/pregnancy outcomes.

The studies evaluated to determine if clinical use of GM-CSF/G-CSF improves embryo development/aneuploidy outcomes include three randomized trials (65–67) and three Level-II studies (two cohort studies (68, 69) and one systematic review) (70). One Level-I study showed no benefit to the euploidy rate (34.8% treatment vs. 33.3% controls) of developing embryos (65). Another large multicenter RCT (N=1,332 unselected women 25-39 years undergoing IVF) demonstrated no improvement in embryo development with GM-CSF treatment vs. controls (normally developed embryos OR 0.98 [0.91–1.05]) (67). One investigation used donated surplus 2-4 cell embryos as a cohort, cultured in media supplemented with 2 ng/ml recombinant human (rh)GM-CSF and observed to blastocyst stage. GM-CSF improved the yield of implantation-competent blastocysts in human IVF (37/49 GM-CSF vs. 15/50 control culture, $P<.0001$) (68). No ETs were performed, making clinical outcomes unevaluable. Another cohort study directly investigated clinical outcomes, but failed to demonstrate improvement in embryo quality, clinical pregnancy rate, or live-birth rate (69). A single RCT that used unfertilized oocytes activated by the calcium ionophore A23187 with or without GM-CSF suggested improved activated embryo development rates and quality (66). However, as calcium ionophores are not used in regular clinical practice and are focused on abnormal fertilization events only, the generalizability is unclear and not clinically applicable. A systematic review in agreement with these data found no improvement in implantation rate and pregnancy rate outcomes (70).

With respect to endometrial thickness, four randomized trials (71–74), five cohort studies (75–79), and three Level-II systematic reviews (80–82) were evaluated for this guideline. Use of G-CSF administered as an intrauterine infusion was not associated with increased endometrial thickness in one Level-I study (72) and show inconsistent association with increased thickness in Level-II studies (75–79). G-CSF was associated with increased endometrial thickness in one Level-I study which focused on women with a thin endometrium (74). These studies are limited by heterogeneous populations, but suggest that G-CSF might benefit patients with recurrent implantation failure or those with an unresponsive endometrium more than unselected populations.

The impact of G-CSF or GM-CSF treatment on IVF outcomes has been evaluated in six randomized trials (67, 71–73, 83, 84), seven cohort studies (75–79, 85, 86), and five Level-II systematic reviews (69, 70, 80–82). Use of G-CSF is associated with improved implantation rate, clinical pregnancy rate, or both in three of five RCTs (71, 83, 84), but live-birth rate was not assessed in any included RCTs assessing G-CSF. The largest multicenter RCT of GM-CSF treatment (N=1,332 unselected women 25-39 years undergoing IVF) demonstrated improved implantation rate (23% vs. 18.7%, $P=.02$) and live-birth rate/transfer (28.9% vs. 24.1%, $P=.03$), with sub-analysis suggesting specific benefit regarding live birth in women with a history of recurrent miscarriage (29.6% vs. 23.1%, $P=.02$) (67). However, the improvement in outcome was only observed in suboptimal

culture conditions (low human serum albumin [HSA] concentration) used in the first 620 subjects and not in the remaining 529 subjects, where a normal (higher) HSA concentration was used. In normal culture conditions, there was no improvement in any pregnancy outcome. Four of seven Level-II/cohort studies did not show improvement in IVF outcome (75–78), and neither did two Level-II systematic reviews (70, 80), while a third Level-II systematic review suggested that a subset of studies with systemic injection demonstrated increased implantation rate and clinical pregnancy rate (87). Two Level-II meta-analyses showed improvement in implantation rate and clinical pregnancy rate with G-CSF, but the difference was more significant in subgroups of patients with a thin endometrium or repeated IVF failure, not for those with normal endometrial thickness (81, 82). It should be noted that there is a high level of heterogeneity among studies, with variations in study foci, doses, treatment types, and lack of adjustment for meaningful confounders. Taken together, additional investigations are warranted to further evaluate the role of G-CSF in selected subgroups, such as women with recurrent implantation failure and thin endometrium where potential benefit exists but is not consistently demonstrated.

Summary Statements

- There is insufficient evidence to recommend for or against local G-CSF to improve endometrial thickness in women with thin endometrium or clinical pregnancy rates with IVF. (From principally Level-I studies of Good quality and Level-II studies of Low and Good quality with inconsistent findings). (Grade C).
- There is insufficient evidence to recommend for or against G-CSF or GM-CSF administered locally or systemically to improve IVF outcomes. (From principally Level-I studies of Good quality and Level-II studies of Low and Good quality with inconsistent findings). (Grade C).

Intravenous Fat Emulsions

Intravenous fat emulsions used for parental nutrition have been shown to inhibit pro-inflammatory mediators (88). In an early murine model, the rate of spontaneous abortion was significantly reduced with the administration of intravenous fat emulsions (89), which is thought to reduce the activity of NK cells within the endometrium.

One RCT has evaluated intravenous fat emulsions as an intervention in 296 women (n=144 in the treatment group, n=152 controls) with unexplained secondary infertility, recurrent spontaneous abortion, and elevated NK cell activity (>12%) (90). This study showed that infusion of intravenous fat emulsions given on the day of oocyte retrieval was associated with a statistically significant increase in ongoing pregnancy rate and live-birth rate (treatment group 37.5% vs. controls 22.4%, $P=.005$), a nonsignificant increase in chemical pregnancy rate, and a nonsignificant reduction in spontaneous abortion rate (90). A prospective cohort study intended as a pilot to investigate the effectiveness of intravenous fat emulsions on outcomes of women aged 40–42 years

undergoing IVF-ET was terminated early because preliminary data showed no live births in the intravenous fat emulsion group and a 30% live-birth rate in the untreated controls (91).

Summary Statement

- There is insufficient evidence to routinely recommend intravenous fat emulsions for infertile women pursuing IVF. (From one Level-I study of High quality and one Level-II study of Low quality). (Grade C).
- Additional studies are needed to identify populations where benefits may exist but are not proven.

Intravenous Immunoglobulin (IVIG)

Anti-inflammatory and immune-modulating properties of intravenous immunoglobulin (IVIG) have been considered as potential treatment for failed IVF and recurrent pregnancy loss given the hypothesized role of inflammatory bias in these conditions. Despite interest, only two small randomized trials (92, 93) have assessed the effect of IVIG administration on IVF outcomes. Additionally, 10 Level-II studies, 7 of which are cohort studies (94–100) and 3 are systematic reviews (101–103), are included in this guideline examine IVIG and IVF.

IVIG was associated with improved implantation rate (treatment group 8/45 [17.7%] vs. placebo 4/61 [6.5%], $P<.05$), but not pregnancy rate (treatment group 6/18 [33.3%] vs. placebo 4/21 [19.1%], not significant [NS]) in one RCT of 39 women with ≥2 very early abortions (<8 weeks) or biochemical pregnancies and ≥3 failed attempts of ET after IVF (93). Another more recent and well-designed Level-I study of 51 women with repeat unexplained IVF failure showed no significant improvement in live-birth rate (treatment group 4/26 [15%] vs. controls 3/25 [12%], $P=.52$); however, there were only seven pregnancies total (92). Seven Level-II studies, showed improvement with IVIG in at least some parameters (95–98, 100–103), but with a very high level of heterogeneity among studies. Six studies showed improved live-birth rate (96–98, 100–102). Two cohort studies employed analysis of NK/NKT cell expansion or T helper (Th)1:Th2 ratio in the peripheral blood for immune stratification of treatment and response (97, 100). One of these studies was observational, retrospective, and with an unusually high live-birth rate (recurrent implantation failure group 80% vs. 17.9%, $P=.0001$; recurrent miscarriage group 96.3% vs. 30.8%, $P=.0001$) (97), while the other study, also retrospective, demonstrated an improvement in implantation rate specifically in patients with elevated Th1:Th2 ratio (45% IVIG vs. 22% control) (100). Given the expense, unclear stratification criteria, and risk associated with use, use of IVIG should be considered only in the context of well-designed prospective trials.

Summary Statements

- There is insufficient evidence to recommend IVIG administration as part of IVF to improve IVF outcomes. (From two Level-I, but underpowered, studies, one Good quality and one Low quality). (Grade C).

- Subpopulations that benefit from treatment may exist, but additional high-quality experimental RCTs are needed to define indications and explore risks and benefits.

Adalimumab

Considerable success in the treatment of autoimmune diseases with disease-modifying agents such as adalimumab (tumor necrosis factor alpha [TNFa] blocking antibody, Humira®) raises hope that patients with abnormally high TNF secretion may benefit from treatment in conjunction with IVF. A single collaborative group of investigators has explored this hypothesis, with interesting, but unreplicated, results (98, 99, 104, 105). These studies employed a Th1:Th2 ratio assessment by flow cytometry (TNFa:interleukin [IL]-10 intracellular ratio after activation by phorbol ester/calcium ionofore) and an NK cell cytotoxicity assay (K562 cell-line killing, indirectly) to stratify patients into a high-TNFa group that was subsequently treated with adalimumab alone or in combination with IVIG compared with a control group, with all patients also receiving a low molecular-weight heparin (LMWH) and low-dose aspirin. One of the reports showed a statistically significant elevation in live-birth rate among patients treated with adalimumab or IVIG compared with controls (50% [3/6] adalimumab vs. 0% [0/5] controls) (98). This was a small study of 75 subfertile women with Th1/Th2 cytokine elevation who were assigned to one of four different arms (assignment was based on laboratory results and patient acceptance of treatment): Group I, 41 patients received both IVIG and adalimumab; Group II, 23 patients received IVIG; Group III, 6 patients received adalimumab; and Group IV, 5 patients received neither IVIG nor adalimumab (98). A different report from the same group correlated the degree of correction of purported Th1:Th2 "abnormality" with implantation rate and live-birth rate, and only with subset selection of patients with "inadequate cytokine suppression" with those where optimal treatment outcome was obtained was there a correlation with implantation rate (104). Finally, their most recent retrospective analysis of this dataset also examined embryo development cohort quality (that the authors term "die-off ratio") and found that treatment with adalimumab eliminated the correlation between cohort quality and implantation rate (105).

Although interesting, these studies suffer from multiple challenges to interpretation. First, they are all retrospective observational studies, where these agents were used without any attempt at randomization or prospective standardization. Second, stability and meaning of clinical Th1:Th2 ratio or NK cytotoxicity assays are poorly defined and not in routine clinical use even among the immunology/rheumatology community. Third, these studies were not conducted in accordance with current standards for human protection (98, 99, 104). Fourth, these investigations had small sample sizes and extensive heterogeneity in treatments and multiple medications (adalimumab, IVIG, LMWH, aspirin, and even dexamethasone). Although the concept and approach are interesting, it is difficult to ascertain what conclusions can be drawn from these studies, beyond the need for both validation of the diagnostic assays used

and a prospective, randomized trial to directly assess the role for TNF inhibitors in IVF (with or without pretreatment immune stratification). Consequently, these therapies should only be used in the context of exploratory, Institutional Review Board (IRB)-approved studies. These trials should also consider risk associated with treatment. While the potential risks associated with short-term use of adalimumab are unknown, long-term use (greater than 12 weeks) has been associated with an increased risk of serious infection and malignancy (106).

Summary Statement

- There is insufficient evidence to recommend adalimumab treatment to improve IVF outcome. (From Level-II studies of Low quality). (Grade C).

Peripheral Mononuclear Cells

Successful embryo implantation requires a receptive endometrium with an optimal level of local inflammation. Aberrant cell signaling leading to immune dysfunction has been implicated in implantation failure, especially in cases of repeated failed IVF-ET. One possible mechanism may involve poor lymphocyte recruitment within the endometrium. Intrauterine infusion of peripheral blood mononuclear cells (PBMC) has been investigated as a possible therapy for patients with recurrent implantation failure, based on the rationale that maternal immune cells are necessary to achieve immune tolerance to embryonic implantation and placentation. While the precise mechanism of action is unclear, one RCT investigated the efficacy of PBMCs (107). This trial randomized patients with a history of repeated implantation failure to receive either autologous PBMCs cultured and instilled into the endometrial cavity prior to transfer or to standard ET, without pretreatment (107). The treatment group experienced a significantly increased clinical pregnancy rate ($P < .05$) and reduced, but not significant, early pregnancy loss rate. However, these findings are limited by the study's small sample size and the lack of a power analysis. Furthermore, the study included only poor-prognosis patients with a history of repeated IVF failure, contributing to potential selection bias and limiting the generalizability of the findings. A second, nonrandomized Level-II study of poor quality suggested that treatment with PBMCs improved live-birth rate in women with more than four failed transfers and in those with endometrial thickness between 7 and 8 mm (108).

Summary Statement

- There is insufficient evidence to recommend intrauterine infusion of autologous peripheral mononuclear cells prior to ET to improve IVF outcome. (From one Level-I study of Low quality and one Level-II study of Low quality). (Grade C).

Seminal Plasma

Instillation of seminal plasma into the uterus and/or cervix at the time of ovum pickup for IVF has been investigated as a

strategy to improve pregnancy rates in fresh ET cycles. In some animal models this step appears essential for ART (109) and has been theorized to improve endometrial receptivity and/or immune tolerance (110, 111).

Available RCTs investigating the use of seminal plasma insemination have all shown a statistically nonsignificant increase in pregnancy rate compared to either placebo or no intervention (112–115). Of these, two showed an increase in implantation rate with administration of seminal plasma, although one increase was statistically significant (34.7% vs. 27.5%, $P=.026$) (112), while the other was not (21.4% vs. 16.9%, $P=.71$) (113). A meta-analysis of seven RCTs showed a statistically significant improvement in clinical pregnancy rate but no significant improvement in ongoing pregnancy or live-birth rate with seminal plasma insemination (116).

Summary Statement

- There is fair evidence that seminal plasma insemination as part of IVF improves clinical pregnancy rate (From Level-I studies of Good and High quality). (Grade B). However, there is fair evidence that it does not improve ongoing pregnancy or live-birth rates. (From underpowered Level-I studies of Good quality). (Grade B).

Spermatozoa, Antibody-free Preparation

Antibody-free preparation of spermatozoa has been investigated as a technique to reduce the potential impact of antisperm antibodies on fertilization rates in couples with antisperm antibody-positive male partners. These investigations were primarily conducted to develop techniques to prevent failed fertilization following conventional insemination prior to the development of ICSI. Antisperm antibodies have been reported in as many as 10% of infertile couples (117), and may impair either sperm transport or zona penetration (118). Both of these mechanisms have been proposed as possible barriers to natural conception and success with intrauterine insemination (IUI) in these couples. However, presence of both immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies is associated with lower fertilization rates in IVF (119, 120).

One RCT of 36 patients assessed the benefit of chymotrypsin-galactose treatment of sperm vs. sperm incubated in culture medium in patients with over 50% antisperm antibodies, IgG, IgA, or both (121). Chymotrypsin-galactose treatment was associated with an improvement in fertilization rate (46.7% vs. 27.3%, $P<.05$) and a nonsignificant increase in pregnancy rate (per patient 32% vs. 18.2%, $P=.34$; per cycle 21.1% vs. 9.5%, $P=.23$), but the percentage of sperm bound with antibodies was not reduced (121). In another study using couples as their own controls, an antibody-free preparation of sperm in a cohort of 18 couples with an antibody-positive male partner undergoing 24 IVF cycles did not improve fertilization rates compared with untreated sperm (122).

Summary Statements

- There is insufficient evidence to support the recommendation either for or against antibody-free preparation of sper-

matozoa in improving IVF outcomes. (From one Level-I study of Low quality and one Level-II study of Low quality). (Grade C). This procedure has been rendered obsolete by the use of ICSI.

Tacrolimus

The establishment of a healthy pregnancy requires maternal immune tolerance to the invading trophoblast to ensure successful implantation and adequate placentation and fetal growth. Th1 and Th2 mediate immune rejection and tolerance, with recurrent implantation failure being associated with a high peripheral blood Th1/Th2 ratio. A Th1 immune response is associated with allograft, as well as embryo, rejection (123, 124). Based on this rationale, a prospective study (125) evaluated the effect of treating patients with recurrent implantation failure with tacrolimus—an immunosuppressive drug that inhibits antigen-induced lymphocytic proliferation, cytotoxic T-cell formation, IL-2 receptor expression, and the production of IL-2 and interferon-gamma. The study included patients with a history of at least five prior failed IVF cycles and elevated peripheral blood Th1/Th2 ratios and compared the outcomes of patients who received 1 to 3 mg tacrolimus 2 days prior to ET. When comparing IVF outcome of treated patients (n=25) and untreated controls (n=17), the treated cohort had significantly higher clinical pregnancy (per ET, treated 64% vs. untreated 0%, $P<.0001$) and live-birth rates (treated 60% vs. untreated 0%, $P<.0001$) (125). These results should be interpreted with caution as the study was subject to selection bias due to lack of randomization and a small sample size.

Summary Statement

- There is insufficient evidence to recommend tacrolimus to improve IVF-ET outcome. (From a single Level-II study of Low quality). (Grade C).

HARMS AND BENEFITS

While short-term use of some of the immunotherapies reviewed in this document (e.g., aspirin and corticosteroids) are unlikely to be associated with long-term harm, for others there are known risks, and a full accounting of these risks must be weighed against any potential benefits. For example, IVIG use has been associated with fever, hypotension, tachycardia, thromboembolic complications, and anaphylactic reactions (126). As a pooled blood product, IVIG use is also associated with an inherent risk of infectious disease. While intravenous fat emulsion infusions are generally well tolerated, jaundice and hyperthermia have been reported (127). Cytokines such as G-CSF are used in healthy donors in the setting of blood and marrow transplantation. In this setting, common side effects associated with systemic administration include bone pain and myalgias (128). Tacrolimus is most commonly used as an immunosuppressant to prevent whole organ rejection. In this setting, known side effects include nephrotoxicity, neurotoxicity, hypertention, and

diabetogenic effects (129). With each of the above agents, risk and side-effect profiles associated with short-term use, such as in the setting of IVF, are poorly characterized.

Beyond the risks to the patient herself with the use of immunotherapy, these agents may cause harm in the present treatment cycle. In a trial of low-dose aspirin vs. untreated controls, the aspirin group required a higher dose of follicle-stimulating hormone prior to oocyte retrieval and had a higher number of immature oocytes (17). Additionally, the authors noted that "the ratio of good quality embryo per retrieved oocytes was strongly unbalanced between the two groups with a clear advantage for the untreated group and, for the treated one, at lower dose of LDA [low-dose aspirin]" (17). Intravenous fat emulsion treatment also may be associated with harm in the present treatment cycle; authors cancelled their study investigating the effectiveness of intravenous fat emulsions on outcomes of women aged 40–42 years undergoing IVF-ET due to no live births in the intravenous fat emulsion group and a 30% live-birth rate in untreated controls (91). While medications such as aspirin and corticosteroids are inexpensive, others such as IVIG and adalimumab are costly, and their use may give false hope to patients who are struggling with infertility. Most of these therapies should only be used under IRB-approved protocols.

CONCLUSIONS

Immunotherapies aimed at improving the likelihood of live birth in IVF treatment have largely proven to be ineffective or have been insufficiently investigated to make definitive recommendations for their use. In some cases, the use of these adjuvants has been associated with improved surrogate outcomes such as clinical pregnancy. However, these studies tend to involve narrowly defined subgroups of patients identified through immunological testing, which frequently is not widely available, reproducible, or recommended. Given the uncertain benefits and meaningful risks of immunotherapy, future studies should focus on well-defined subgroups where potential for benefit exists but is not consistently demonstrated. A careful assessment of risks associated with therapy must be undertaken in the design of adequately powered RCTs investigating immunotherapies as adjuvants in ART treatment. These investigations should focus on the outcome of live birth. If benefit is demonstrated, then the evaluation of cost-effectiveness is a priority given the high cost of some immunotherapy treatments.

UNANSWERED QUESTIONS

- Future studies of adjuvant immunotherapy in IVF should be adequately powered for the primary outcome of live birth and focus on populations where the potential for benefit exists, but has not been conclusively demonstrated, including conditions such as implantation failure and recurrent miscarriage.
- Side-effect profiles for immunotherapies should be carefully documented in subsequent RCTs.
- Subsequent RCTs investigating immunotherapies should focus on a single agent within a given study. Ideally, these

investigations would be multicenter in order to increase the generalizability of the trial results. Immunological testing as part of these trials should be standardized to improve reproducibility of findings.

- G-CSF/GM-CSF should be reserved for investigational trials in selected subpopulations.
- Until clear and consistent relationships are demonstrated between immunophenotypes and ART outcomes, routine immunological testing in the general ART population cannot be recommended.

SUMMARY

- Given the lack of evidence to support improved IVF outcomes, there is 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. (From Level-I studies of Good and High quality). (Grade A).
- There is good evidence to recommend against the routine use of corticosteroids during stimulation to improve the outcome of live birth in ART cycles in the general population. (From principally Level-I studies of Good quality). (Grade A).
- There is good evidence to recommend against the routine use of corticosteroids during the implantation window to improve the outcome of live birth in ART cycles in the general population. (From principally Level-I studies of Good quality). (Grade A).
- There is insufficient evidence to recommend for or against local G-CSF to improve endometrial thickness in women with thin endometrium or clinical pregnancy rates with IVF. (From principally Level-I studies of Good quality and Level-II studies of Low and Good quality with inconsistent findings). (Grade C).
- There is insufficient evidence to recommend for or against G-CSF or GM-CSF administered locally or systemically to improve IVF outcomes. (From principally Level-I studies of Good quality and Level-II studies of Low and Good quality with inconsistent findings). (Grade C).
- There is insufficient evidence to routinely recommend intravenous fat emulsions for infertile women pursuing IVF. (From one Level-I study of High quality and one Level-II study of Low quality). (Grade C).
- There is insufficient evidence to recommend IVIG administration as part of IVF to improve IVF outcomes. (From two Level-I, but underpowered, studies, one Good quality and one Low quality). (Grade C).
- There is insufficient evidence to recommend adalimumab treatment to improve IVF outcome. (From Level-II studies of Low quality). (Grade C).
- There is insufficient evidence to recommend intrauterine infusion of autologous peripheral mononuclear cells prior to ET to improve IVF outcome. (From one Level-I study of Low quality and one Level-II study of Low quality). (Grade C).
- There is fair evidence that seminal plasma insemination as part of IVF improves clinical pregnancy rate (From Level-I studies of Good and High quality). (Grade B). However,

there is fair evidence that it does not improve ongoing pregnancy or live-birth rates. (From underpowered Level-I studies of Good quality). (Grade B).

- There is insufficient evidence to support the recommendation either for or against antibody-free preparation of spermatozoa in improving IVF outcomes. (From one Level-I study of Low quality and one Level-II study of Low quality). (Grade C). This procedure has been rendered obsolete by the use of ICSI.
- There is insufficient evidence to recommend tacrolimus to improve IVF-ET outcome. (From a single Level-II study of Low quality). (Grade C).

RECOMMENDATIONS

- Immunotherapies reviewed in the present document are either not associated with improved live-birth outcome in IVF or have been insufficiently studied to make definitive conclusions regarding benefits and risks. In the absence of well-designed adequately powered RCTs, patients must be informed of uncertain benefits and risks associated with immunotherapy.
- There is no evidence to suggest screening for these conditions in an asymptomatic population.

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