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Adjuvants therapies for women undergoing IVF: is there any evidence of their safety and efficacy? an updated mini-review

Abstract

In the last two decades a series of adjuvant therapies have been proposed to improve the success of IVF and most of them are currently prescribed even though the quality of scientific evidence supporting their efficacy in improving live birth rates after IVF is weak. The aim of this paper is to describe some of the therapies mostly used by women undergoing IVF such as dehydroepiandrosterone, testosterone, low-dose aspirin, low-molecular-weight heparin (LMWH), corticosteroids and endometrial scratching, and to assess the current evidence about their safety and efficacy.

Keywords: Adjuvants, IVF, Ovarian response, Endometrial receptivity, Dehydroepiandrosterone, Testosterone, Aspirin, Heparin, Corticosteroids, Endometrial Scratching, Injury, Biopsy

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Introduction

Patients undergoing in vitro fertilization (IVF) are usually offered adjuvant therapies in order to increase the probability of having a live birth, especially after failed attempts, however, in most of the cases they have not previously been tested for their efficacy and safety in randomized control trials (RCT). If such preliminary studies have not been conducted it is possible that a useless therapy or even a therapy leading to adverse health outcomes may be introduced, generating a "therapeutic illusion".[1] In this review we discuss some of the adjuvants usually offered at this time to women undergoing IVF, gathering them together into two main groups: adjuvants for poor ovarian response or adjuvant for endometrial receptivity, searching for evidence of their safety and efficacy.

Adjuvants for ovarian response

Approximately 5-18% of IVF cycles in which women undergo controlled ovarian stimulation (COS) result in poor ovarian response, ending up with an unsatisfactory outcome of about 2-4% pregnancy rate.[2] This negative outcome can be associated to different factors such as maternal age, body mass index, genetic predisposition and ovarian dysfunctions. In order to improve this result, the use of androgens such as dehydroepiandrosterone or testosterone has been proposed as adjuvant for ovarian response to the follicle-stimulating hormone (FSH).

Dehydroepiandrosterone (DHEA)

DHEA, also known as androstenolone, is an an androgen prehormone, a precursor to the sex hormones testosterone and estradiol, produced in women in the adrenal glands and in ovarian theca cells. It is the most abundant circulating steroid hormone in humans, however, its level show a marked decrease in women after 45 years of age.[3] It can be administered as a dietary supplement and its first use as adjuvant treatment for assisted reproduction was reported by Casson et al.,[4] indicating that it could improve ovarian response to COS in patients classified as "poor responders" improving the blood insulin growth factor-1 (IGF-1) level, which in turn may improve the effect of gonadotrophins in stimulating follicular development, and augmenting estradiol production in granulosa cells, acting as a precursor to androstenedione and testosterone in the theca cells.[4] Successively, it has been proposed for a category of women such as those affected by premature ovarian failure (POF), premature ovarian aging (POA), diminished ovarian reserve (DOR) as defined by the Bologna criteria[5] and in women with increased stimulating hormone (FSH).[6] Some authors reported increased number of oocytes retrieved and improved embryo quality,[7,8] low aneuploidyrate,[9] higher pregnancy rates[10] and increased spontaneous pregnancies in patients with POF (27 Mamas, 2009a) and high AMH levels,[2,11] however no positive effect was found when women with normal ovarian reserve were treated with DHEA.[12] The beneficial effect of the use of DEA for women with DOR undergoing IVF has been mainly reported by retrospective studies, while results from recent meta-analyses and randomized control trials showed that DHEA pre-treatment did not improve clinical pregnancies. Li et al.,[13] analysed the effect of DHEA in women undergoing IVF/ICSI treatment for DOR including in their meta-analysis RCTs, case–control studies and self-controlled studies for a total of eight studies analyzed. Their results showed that the use of DHEA increased the clinical pregnancy rate (Relative Risk (RR) 2.13; 95% CI 1.12–4.08). Similar results were obtained in subgroup analyses including randomized controlled trials and case–control studies (RR 2.57; 95% CI 1.43–4.63) and self-controlled studies (RR 3.95; 95% CI 1.28–12.19). However, the effects of DHEA on oocyte retrieval, implantation, and abortion were not significant. The Cochrane review conducted in 2015 showed higher ongoing pregnancy rates or live birth rates following the pre-treatment with DHEA. Nevertheless, no benefit was observed when studies with high risk of bias were excluded.[14,15] Finally, a third meta-analysis analysing the effect of DHEA in women with DOR including a total of nine studies, four RCTs, four retrospective and one prospective concluded that clinical pregnancy rates were increased significantly in DOR

patients who were pre-treated with DHEA (OR = 1.47, 95% CI: 1.09-1.99), whereas no differences were observed in the number of oocytes retrieved, the cancellation rate of IVF cycles and them is carriage rate between the cases and controls (WMD= −0.69, 95% CI: −2.18-0.81; OR = 0.74,95% CI: 0.51-1.08; OR = 0.34, 95% CI: 0.10-1.24). However, restricting the analysis to only RCTs, a non-significant difference in the clinical pregnancy rate was observed(OR = 1.08, 95% CI: 0.67-1.73).[15]

Conclusive statement

Although the effect of DHEA on improving ovarian response seems to be promising, there is insufficient evidence to recommend DHEA supplementation at this time. Furthermore, the long-term risk of DHEA administration remain unknown. More RCTs with large sample size are needed to obtain good quality evidence on its safety and efficacy.

Testosterone (TT)

Testosterone is a downstream molecule in the steroidal pathway from DHEA. It can be administered either trans-dermally or orally. Different RCTs report a beneficial effect of TT pre-treatment[16,17] and the meta-analysis from Bosdou et al.[18] analyzing both trials conducted by Massin et al.[16] and Kim et al.[17] reported that pretreatment with transdermal testosterone was associated with an increase in clinical pregnancy (risk difference (RD): +15%, 95% confidence interval (CI): +3 to +26%) and live birth rates (RD: +11%, 95% CI: +0.3 to +22%) in poor responders undergoing ovarian stimulation for IVF. A second meta-analysis conducted by Gonzalez-Comadran et al.[19] also reported that testosterone-treated women achieved a significantly higher live birth rate (risk ratio, RR, 1.91, 95% CI 1.01 to 3.63), clinical pregnancy rate (RR 2.07, 95% CI 1.13 to 3.78) and required significantly lower doses of FSH (RR -461.96, 95% CI -611.82 to -312.09). However, differences observed in clinical pregnancy per embryo transferred were not statistically significant (RR 1.72, 95% CI 0.91 to 3.26). Authors did not observe any difference regarding number and quality of the oocytes retrieved.[19]

Conclusive statement

The data are still insufficient to recommend TT administration to improve the probability of pregnancy in poor responders undergoing ovarian stimulation for IVF.

Adjuvants for endometrial receptivity

Despite the substantial progress in the treatment of sub-fertile couples over the last two decades, endometrial receptivity remains a key limiting factor for implantation after IVF. The role of the immune system is well recognized to be essential for embryo implantation, establishing receptivity and achieving pregnancy: it facilitates tolerance for the foreign embryo modulating decidual response, epithelial embryo attachment, trophoblast invasion and promotes vascular adaptation to support placental morphogenesis.[20,21] Different adjuvants have been proposed in order to improve the immune response, here we report the drugs most used for this purpose.

Low-dose aspirin

Low-dose aspirin is widely used for prevention of cardiovascular diseases, however, it has been also used as adjuvant for women undergoing IVF in order to increase their chance of live birth due to its anti-inflammatory, vasodilatory, antiplatelet aggregation properties. Although its beneficial effects are widely recognised, aspirin administration has also been associated with miscarriage and vaginal bleeding. Generally, aspirin is administrated to patients immediately at the start of down-regulation, while there is contradictory evidence on the appropriate duration of the treatment. Literature includes many articles with mixed results concerning the effect of this adjuvant. One of the first Cochrane reviews about aspirin administration found that when combined with unfractionated heparin it may prevent recurrent miscarriage (RM) in women with anti-phospholipid syndrome.[22] On the contrary, in a more recent meta-analysis of 4 trials, authors showed that LBRs did not improve and early miscarriage rates did not decline by the addition of heparin to low-dose aspirin in women with congenital thrombophilia.[23] Similar findings were observed in the latest Cochrane review evaluating the effectiveness and safety of aspirin in women undergoing ART.[24] Authors included a total of thirteen studies, tenadministrating a daily dose of 100 mg and three using 80 mg of aspirin per day. In most of them, aspirin was commenced immediately at the start of down-regulation, while the duration was variable. Eight studies provided a placebo for the control group. Also in this case, authors showed no evidence of a difference between the aspirin group and the group receiving no treatment or a placebo in rates of live birth (RR 0.91, 95% CI 0.72 to 1.15, 3 RCTs, n = 1053, I^2 = 15%, moderate-quality evidence). In addition, clinical pregnancy rates were also similar for the two groups (RR 1.03, 95% CI 0.91 to 1.17, 10 RCTs, n = 2142, I^2 = 27%, moderate-quality evidence); sensitivity analysis, excluding studies at high risk of bias, did not change the effect estimate. Moreover, there was no evidence of a difference between groups in terms of miscarriage (RR 1.10, 95%CI 0.68 to 1.77, 5 RCTs, n = 1497, I^2 = 0%, low-quality evidence), ectopic pregnancy (RR 1.86, 95% CI 0.75 to 4.63, 3 RCTs, n = 1135, I^2 = 0%, very low quality evidence) or vaginal bleeding (RR 1.01, 95% CI 0.14 to 7.13, 1 RCT, n = 487, very low quality evidence). Data concerning the use of aspirin for preventing hypertensive disorders in pregnancy are controversial as well. A RCT found such a benefit in the use of aspirin for the prevention of hypertensive complications of pregnancy,[25] however, a recent meta-analysis with individual patient data did not recommend the low-dose aspirin for hypertensive complications and preterm delivery after IVF.[26] One study found low incidence of ovarian hyperstimulation syndrome in patients receiving low-dose aspirin.[27]

Conclusive statement

Currently there is no evidence in favor of routine use of aspirin in order to improve pregnancy rates for a general IVF population or in cases of RIF. Moreover, adverse effects such as vaginal bleeding have been reported by different authors. Based on current evidence, aspirin should therefore be offered only in selected cases.

Heparin

Heparin is a drug used as a blood thinner in order to treat or prevent different diseases such as vein thrombosis, pulmonary embolism and arterial thromboembolism. In the last decade it has been proposed also as an adjunct in assisted reproduction since it has been speculated that heparin may improve the intrauterine environment in sub-fertile women. The proposed mechanism is that heparin may improve decidualization with an associated activation of growth factors such as IGF-1, heparin-binding epidermal growth factor and cytokine expression in the endometrium promoting embryo implantation through trophoblast invasion and proliferation, promoting successful pregnancy.[28,29] Heparin is administered trans-dermally in the form of unfractionated or low-molecular-weight heparin (LMWH) which is derived from heparin by depolymerization, showing similar activity

but with increased bioavailability and half-life. It is given at or after egg collection or at embryo transfer(peri-implantation heparin). Different studies have shown that there is no evidence regarding the efficacy of heparin either in women with two or more consecutive previous pregnancy losses[30] or in those with unexplained recurrent miscarriage[31] or in women with inherited thrombophilia (TanWK). Also Seshadri et al.[32] in their meta-analysis including 10 relevant studies (five observational and five randomized) did not observe any difference analysing only randomized studies with regard to clinical pregnancy rate (RR 1.23, 95% CI 0.97–1.57), live birth rate (RR 1.27, 95% CI 0.89–1.81) implantation rate (RR 1.39, 95% CI 0.96–2.01) and miscarriage rate (RR 0.77, 95% CI 0.24–2.42) between women receiving heparin compared to placebo during IVF treatment. On the contrary, a systematic review and a meta-analysis including two RCTs and one quasi-randomized trial showed a significant improvement in the LBR (risk ratio (RR) ¼ 1.79, 95% confidence interval (CI) ¼ 1.10–2.90, P ¼ 0.02) and a reduction in the miscarriage rate (RR ¼ 0.22, 95% CI ¼ 0.06–0.78, P ¼ 0.02) with LMWH compared with controls. However, the beneficial effect of LMWH was not significant when only studies with unexplained RIF were pooled.[28] Finally, a recent Cochrane review[33] including three RCTs, of which two consisted of women with 3 RIF and one consisted of women with unexplained infertility undergoing their first IVF cycles, reported similar findings: when a fixed effect analysis was used as a statistical model, peri-implantation heparin was associated with an improvement in live birth rate compared with placebo or no heparin (odds ratio (OR) 1.77, 95% confidence interval (CI) 1.07 to 2.90) and also an improvement in the clinical pregnancy rate (OR 1.61, 95% CI 1.03 to 2.53) but authors noted low quality of evidence. While, when a random effects model was used, no difference was noted between the groups for either live birth (OR 1.85, 95% CI 0.80 to 4.24) or clinical pregnancy (OR 1.66, 95% CI 0.94 to 2.90).

Adverse events are poorly reported in studies evaluating the effect of heparin in women undergoing IVF or when reported they are not suitable for analysis and so no firm conclusions could be drawn regarding adverse effects. However, events of bleeding, bruising and thrombocytopenia have been described and it appeared that they were increased when heparin administration was received over a longer period.

Conclusive statement

There is insufficient evidence to recommend heparin as an adjuvant therapy during IVF treatment at this time. Furthermore, side effects have been reported with use of heparin and no firm conclusions can be drawn regarding its safety. Therefore, it should be prescribed only when clinically indicated after proper counselling. More well-designed, powered, double-blind, randomized, placebo-controlled, multicenter trials are needed to obtain good quality evidence on its safety and efficacy.

Corticosteroids

Uterine receptivity is controlled by locally-acting growth factors such as natural killer (NK) cells and cytokines[35-38] Defects in the integrity of cytokine network and an excess of NK cell activity have been implicated in implantation failure and recurrent miscarriage.[38-40] Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex with potent anti-inflammatory and immunosuppressive properties including generation, differentiation and function of immune cells with profound consequences for tolerance and immunity.[41,42] Glucocorticoids in particular have been proposed to improve the embryo implantation rate after IVF and protect against miscarriage by acting as immunomodulators to reduce the NK cell count to the normal range,[43] normalizing the cytokine expression profile in the endometrium and by suppression of endometrial inflammation.[44-46]

A variety of drugs are available for administration from embryo implantation through the early placentation phase, ranging from prednisolone, methylprednisolone and dexamethasone to hydrocortisone combined with prednisolone and different protocols have been proposed, however, dose schedules and duration of treatment vary enormously.[47]

The latest Cochrane review concerning the use of corticosteroids in ART was published in 2012[47] and it investigated whether the administration of glucocorticoids around the time of implantation improved clinical outcomes in women undergoing IVF or ICSI. The meta-analysis included fourteen studies (involving 1879 couples) and found no evidence that glucocorticoids helped to improve live birth rates (OR 1.21, 95% CI 0.67 to 2.19). With regard to pregnancy rates, there was also no evidence that glucocorticoids improved clinical outcome (13 RCTs; OR 1.16, 95% CI 0.94 to 1.44). However, there was some evidence of increased pregnancy rates among women undergoing IVF and not ICSI (6 RCTs; OR 1.50, 95% CI 1.05 to 2.13), but authors noted a borderline statistical significance. These findings were limited to the routine use of glucocorticoids and cannot be extrapolated to women with autoantibodies, unexplained infertility or recurrent implantation failure. In women with recurrent miscarriage, prednisolone treatment was demonstrated to decrease expression of angiogenic factors and decrease vessel maturation in non-pregnant endometrium[48] and corticosteroids alone or in combination with low-dose aspirin are reported to improve pregnancy rate after IVF in women with antinuclear antibodies, anti-cardiolipin antibodies, anti-thyroid antibodies or lupus anticoagulant.[44,50] It has been reported that glucocorticoid excess in pregnancy can cause adverse effects in the placenta, fetal growth restriction and altered fetal development,[51] however, adverse events are poorly reported by authors and data in the literature are conflicting. Studies in humans demonstrate that high circulating levels of endogenous maternal cortisol during pregnancy correlate negatively with birthweight and program higher blood pressure, altered brain structure and behavioral disorders in children.[52] Few studies have followed up the outcomes of corticosteroid use in IVF treatment for infant health, but those that do report perinatal outcomes raise concerns for potential adverse effects on fetal development.[53] On the contrary, Krigstein & Sacks[46] showed relatively low incidence of serious adverse outcomes in women who naturally conceive while utilizing corticosteroid therapy for immune disorders, and conclude from analyses of fetal congenital malformations that corticosteroids do not present a major teratogenic risk. In a prospective controlled study of 311 pregnancies with systemic use of glucocorticoids spanning the first trimester, a 64% increase in miscarriage and 2.1-fold increase in preterm births were observed compared to the control[54] and an earlier study of 66 pregnant women with autoantibodies and recurrent miscarriage administered prednisone in combination with aspirin for the duration of pregnancy showed elevated risk of hypertension, diabetes mellitus and premature birth.[55] Long-term follow-up studies of children born after first trimester glucocorticoid administration are definitely required to elucidate possible effects on cardiometabolic and neuroendocrine development, with accurate analysis of dose and duration of treatment.

Conclusive statement

To date, there are no well-controlled, sufficiently powered clinical trial data to demonstrate the efficacy of peri-implantation

corticosteroid therapy in unselected women undergoing assisted reproduction. Prednisolone, the glucorticoid drug most used as adjuvant for endometrial response, maintains a Category D rating with the Food and Drug Administration in the USA as "there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks", which indicates routine administration is not indicated. There may be justification for continued exploratory investigation of glucorticoids in fertility disorders with specific and defined immune aetiologies that are demonstrably responsive to corticosteroid therapy. Further well designed randomized studies are required to elucidate whether and which specific subgroups of women may be responsive to glucocorticoid treatment.

Endometrial scratching (injury/biopsy)

The concept that endometrial injury could improve endometrial receptivity arises from the observation that pregnancy rate was enhanced in women performing hysteroscopy together with curettage. The first paper reporting the potential beneficial effect of endometrial biopsy was published by Karow et al.[56] who observed that there were only two miscarriages in 28 women who underwent in the luteal phase and conceived in the same cycle.[56] The rationale behind the practice of endometrial scratching is that it has been demonstrated that mechanical manipulation of the endometrium induces the secretion of several pro-implantation chemical factors including cytokines and growth factors such as leukemia inhibitory factor, interleukin-11, and heparin-binding epidermal growth factor (EGF)-like growth factor and stimulates a better decidual reaction.[57] This procedure is commonly performed some time prior to embryo transfer using a pipelle or similar device, introducing it into the vagina reaching the uterine fundus and sampling a piece of endometrium by suction and rotation within the uterine cavity. Even though hundreds of papers have been published on this topic, the number of RCTs is few and the day in which to perform the procedure varies enormously. Some studies performed multiple endometrial sampling at different stages of endometrial development e.g. on days 8,12,21 and 26 through the proceeding cycle before IVF[58] or only on days 21 and 26 of the proceeding cycle.[59] However, Hayashi et al.[60] showed that a single sampling in the proliferative phase was found adequate to improve reproductive outcomes because a single, site-specific hysteroscopic biopsy-induced injury applied on the posterior endometrium at the midline, 10 to 15 mm away from the fundus on days 4 to 7 of the IVF cycle, improved results in six patients.[60]

The latest Cochrane review investigating the effectiveness and safety of endometrial injury performed before embryo transfer in women undergoing ART was published in 2015.[61] It included a total of 14 trials: thirteen studies comparing endometrial injury performed between day 7 of the previous cycle and day 7 of the embryo transfer (ET) cycle versus no injury, and one study comparing endometrial injury on the day of oocyte retrieval versus no injury. In the studies comparing endometrial injury performed between day 7 of the previous cycle and day 7 of the ET cycle, the intervention was associated with an increase in live birth or ongoing pregnancy rate in women with previous implantation failures: RR 1.42, 95% confidence interval (CI) 1.08 to 1.85; P value 0.01. In this group, endometrial injury was also associated with an increased clinical pregnancy rate: RR 1.34, 95% CI 1.21 to 1.61; P value 0.002; 13 RCTs. No difference in the result was observed performing a sensitivity analysis removing the studies at high risk of bias. There was no evidence of an effect on miscarriage, however the evidence is of low-quality. On the contrary, results from the only RCT comparing endometrial injury on the day of oocyte retrieval versus intervention, reported that endometrial injury markedly decreased live birth (RR 0.31, 95% CI 0.14 to 0.69; P value 0.004; 156 women; low quality evidence) and clinical pregnancy (RR 0.36, 95% CI 0.18 to 0.71; P value 0.003; one RCT; 156 women; low-quality evidence),.[61]

Another systematic review and meta-analysis comparing the efficacy of endometrial injury versus no intervention in women with RIF undergoing IVF and including seven controlled studies (four randomized and three non-randomized), showed that local endometrial injury induced in the cycle preceding ovarian stimulation is 70% more likely to result in a clinical pregnancy as opposed to no injury.[62] Results showed that that endometrial injury by hysteroscopy catheter yielded a RR of 1.51 (95% CI: 1.30–1.75) while endometrial sampling with biopsy showed a RR of 2.32 (95% CI:1.72–3.13) for clinical pregnancy. Finally, a third meta-analysis of two randomized and six non-randomized controlled studies including women who had at least one failed IVF cycle showed that clinical pregnancy rate was significantly improved after endometrial injury in both the randomized (relative risk, RR, 2.63, 95% CI 1.39-4.96, P=0.003) and non-randomized studies (RR 1.95, 95% CI 1.61-2.35, P<0.00001).[63] However, the improvement did not reach statistical significance in the one randomized study which reported the live birth rate (RR 2.29, 95% CI 0.86-6.11).

Conclusive statement

Current evidence suggests some benefit of endometrial injury performed during the month before the start of ovarian stimulation in women with unexplained RIF while local injury on the day of oocyte retrieval has a negative impact on both clinical PR, ongoing PR and live birth rates. Furthermore, there is no evidence of effect on miscarriage or bleeding, it appears only to cause some pain, although short lived.

However, well- designed RCTs stratifying the results for women with and without recurrent implantation failure (RIF) and reporting live births are required in order to assess if this practice should be proposed to all women undergoing IVF or it should be limited to women with RIF. Moreover, timing of intervention, phase in which the procedure should be performed and the benefit of multiple or single biopsy should still be elucidated.

Conclusion

The quality of scientific evidence on the safety and efficacy of the adjuvants described in this review in improving live birth rates after IVF is very low. Although some of the adjuvants discussed may have a promising future, more robust, well designed and randomized studies are required to elucidate whether and which specific subgroups of women may benefit from their use. In the light of this, clinicians should advise patients about these options with caution, warning them about potential side effects and considering their real validity before charging them to patients.

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Conflicts of Interest

The corresponding author discloses any potential conflict of interests for any of the submitting authors, in reference to the submitted material.

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