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Use of Adjuvants in INFERTILITY

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CHAPTER

2

Various Options of Additional Therapy in In Vitro Fertilization with Best Available Evidence for Each Suggested Therapy: An Overview

Madhuri Patil

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INTRODUCTION

We need to optimize the results of assisted reproductive technology (ART), as even after 40 years of in vitro fertilization (IVF) treatment and research there is only marginal improvement in implantation and pregnancy rates, though major progress has been made in improving stimulation protocols and fertilization procedures, optimizing embryo culture conditions, and preventing premature luteinization.

Thirty percent of the embryos are lost at preimplantation stage, another 30% are lost after embryos implant but prior to missed period which is detectable by positive beta-human chorionic gonadotropin (hCG) and 10% are lost after the missed period.[1] Disturbance in the embryo–maternal dialog is the major reason for 60% of all pregnancies terminated at end of the peri-implantation period.

As even failure of the first cycle can be devastating, we need to optimize the results after ART and thus comes the role of adjuvants in IVF. Adjuvants are substances or therapies that help and enhance the effect of a drug, treatment, or biologic system.

ADD-ONS IN IN VITRO FERTILIZATION PROGRAM

The add-on or adjuvant therapies could be pharmacological or nonpharmacological agents, surgical procedures, or additional interventions in the IVF laboratory **(Table 1)**.

Before advising these therapies, one must remember that they should be chosen with great care as they are expensive with questionable actual advantage.

Pharmacological Adjuvants

An adjuvant is a substance that enhances the pharmacological effect of a drug.

TABLE 1: Adjuvant therapies in ART.

Adjuvants	*Therapies*
Pharmacological adjuvants	• To optimize ovarian response • *Adjuvants in treatment of poor responders*: – Growth hormone (GH)/GH-releasing factor (GHRF) – Pyridostigmine – DHEA/testosterone – Aspirin – L-arginine – Aromatase inhibitors – Estrogen pretreatment – GCSF • *Adjuvants in treatment of PCOS*: – Glucocorticoids—prednisone, methylprednisolone, and dexamethasone – Metformin – Myoinositol – N-acetylcysteine – Melatonin – Vitamin D – Chromium polynicotinate • *To optimize ART outcome*: – Antioxidants—coenzyme Q10 – Micronutrients – Dopamine agonist – Aspirin – Heparin – Immune therapy – Vasodilators—sildenafil – Calcium ionophores
Nonpharmacological adjuvants	• Acupuncture • Acupressure • Massages • Reiki • Hypnosis

Contd...

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Adjuvants	*Therapies*
Surgical adjuvants	• Routine hysteroscopy • Endometrial scratch • Hysteroscopic removal of polyps and submucous myoma, septum • Removal or disconnection of hydrosalpinx • Management of ovarian endometrioma • Laparoscopic ovarian drilling
New technologies	• Advanced sperm selection procedures • Time-lapse embryo monitoring • Preimplantation genetic screening • Assisted hatching • Use of embryo glue

(ART: assisted reproductive technology; DHEA: dehydroepiandrosterone; GCSF: granulocyte colony-stimulating factor; PCOS: polycystic ovary syndrome)

Adjuvants to Enhance In Vitro Fertilization Outcome in Poor Responders

Adjuvants in poor responders can modify the intraovarian environment.

- *Growth hormone (GH)*: GH enhances gonadotropin effects on granulosa cells (GCs) and its action on the liver, increasing insulin-like growth factor-1 (IGF-1) systemically, which in turn will act on the follicle resulting in oocyte maturation and enhanced follicle growth and steroidogenesis.[2] IGF-1 synergizes with follicle-stimulating hormone (FSH) in its effect in inducing GC aromatase activity and also stimulates thecal androgen production, synergizing with luteinizing hormone (LH). Beneficial effect of GH is also seen on the probability of clinical pregnancy rate (CPR) and live birth rate (LBR) in women with decreased ovarian reserve (DOR) and poor responders.[3-6] However, no improvement in LBR was noted in the presence of previous suboptimal response to controlled ovarian stimulation (COS).[5] The most recent publication has shown no statistically significant benefit on CPR, LBR, and ongoing pregnancy rate.[7] The role of GH to treat a woman with a poor response to ovarian stimulation cannot be supported on the basis of the available evidence.[8-10]
- *Growth hormone-releasing factor (GHRF)*: Earlier reports showed that GHRF when given in the dose of 500 µg twice daily enhances gonadotropin-induced steroidogenesis, cyclic adenosine monophosphate (cAMP) formation. It also increases GH and IGF-1 concentration, thus improves the ovarian response to gonadotropins.[11,12] However, a large multicentric, prospective, randomized, double-blind, placebo-controlled trial (196 patients) showed no beneficial effect on the CPR, LBR, and cycle cancelation rate.[12] GHRF also had no beneficial effect on the outcome and had no significant effect on mean number of follicles with a diameter of ≥16 mm, days of stimulation, and total dose of gonadotropin required.[12]
- *Addition of pyridostigmine*: Pyridostigmine is an acetylcholinesterase inhibitor, when given in the dose 120 mg/day orally can increase GH secretion by enhancing the action of acetylcholine.[13] Addition of pyridostigmine does not improve the ongoing pregnancy rate or LBR in poor responders undergoing IVF.[14] However, Chung-Hoon et al. in 1999 reported beneficial effect of pyridostigmine on total dose of gonadotropins (38.4 ampoules vs. 48.3 ampoules), number of oocytes retrieved (5.9 vs. 3.7), and CPR (25.7% vs. 11.4%).[15]
- *Androgens pretreatment*: Androgens increase FSH receptor expression in GCs, stimulating IGF-1, which may have a beneficial effect on the number of small antral follicles and also improve the ovarian sensitivity and responsiveness to FSH.[16-19] Use of transdermal testosterone or dehydroepiandrosterone (DHEA) pretreatment in poor responders undergoing COS for ART is safe and effective way of increasing the intraovarian androgen concentration.[20,21] Androgens decrease the dose of gonadotropin required and duration of stimulation and also increase in the number of cumulus-oocyte complexes (COCs) retrieved.[22] Transdermal testosterone pretreatment at a dose of 10 mg/day for 21 days was associated with decreased duration and total dose of gonadotropin, increased number of COCs retrieved, and an increased CPR (+15%) and LBR (+11%).[22] The same author in 2016 concluded that testosterone did not increase the number of COCs retrieved by >1.5 in poor responders and there was also no increase in LBR.[23]
  - *Dehydroepiandrosterone administration*: Marked heterogeneity of treatment group made a firm conclusion on therapeutic efficacy of DHEA difficult. The rationale for its use is related to decline of DHEA in older women that contributes to the reduced circulating and intraovarian testosterone. Administration of DHEA can have a direct effect on the aging ovary by increasing the pool of follicles up to the preantral stage. It can also reduce apoptosis of the originally recruited follicles and affect the nondysfunctional events happening during meiosis. DHEA can also improve steroidogenesis, since it is a precursor of estradiol and testosterone[24] and may influence ovarian follicular growth by serving as ligands for androgen receptors.[24]

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First use of DHEA was reported by Casson PR et al. in 2000[20] in patients aged 35–40 years and having normal FSH concentrations. He concluded that DHEA can augment response to ovulation induction in poor responders with higher number of follicles >15 mm and peak estradiol value, though much difference in the gonadotropin dose was not noted.[25,26] Barad et al., 2007 and Hyman et al., 2010 reported increased oocyte yield (4.4 + 0.5 vs. 3.4 + 0.5; P: 0.05), higher fertilization rate (67% vs. 39%; P: 0.001) and higher embryo grade (3.4 + 0.09 vs. 2.9 + 0.1; P: 0.02), increased pregnancy rate (28.4% vs. 11.9%; P: 0.05), and significantly lower miscarriage rates following DHEA supplementation. Mamas and Mamas, 2009[27] (5 patients) and Sönmezer et al., 2009[28] (19 patients) in addition to the above also reported increased number of metaphase II oocytes (4 + 1.8 vs. 2.1 + 1.8; P: 0.05), increased number of day 3 high quality embryos (1.9 + 0.8 vs. 0.7 + 0.6; P: 0.05), and higher pregnancy rates (47.4% vs. 10.5%; P: 0.01). Wiser et al. also showed a beneficial effect on the LBR.[29]

Dehydroepiandrosterone supplementation also increased anti-Müllerian hormone (AMH) levels in patients with DOR in parallel with the duration of use and increase was more prominent in younger women.[30-34] These women who had an increase in AMH levels were more likely to become pregnant and also showed a lower rate of embryonic aneuploidy in the DHEA group (38.2% vs. 61%) as detected by preimplantation genetic screening (PGS).[33,34] This increase in AMH was not validated by other authors.[35,36] Benefit after DHEA was seen only after it was given for an average of 8.5 weeks.[29] As most these studies which showed benefit were mostly small case series, there were several other studies that showed conflicting results and have suggested large-scale, well-designed confirmatory randomized controlled trials (RCTs) to prove the efficacy of DHEA before it can be recommended for routine use.[22,37-39]

Zhang M et al.,[40] J Assist Reprod Genet, April 2016, concluded based on the limited available evidence that DHEA supplementation seems to improve antral follicle count, AMH, oocyte number, implantation rate, CPR, and LBR in patients with poor ovarian reserve (POR). However, he also suggested further research to clarify the effect of DHEA exposure in ART.

The Cochrane review in 2015 concluded that androgen supplementation prior to ovarian stimulation is not supported by the best available evidence though it may be associated with improved LBR.[41] This review also said that there is insufficient evidence to draw any conclusions about the safety of either androgen. Although some scientific evidence seems to support the use of androgen pretreatment in POR, several authors have recommended further studies for its use.[42,43]

- *Aspirin*: Administration induces a shift from thromboxane A2 to prostacyclin, leading to vasodilatation and increased peripheral blood supply. A meta-analysis to determine the effect of low-dose aspirin versus placebo or no treatment on the likelihood of clinical outcomes in IVF/intracytoplasmic sperm injection (ICSI) cycles was conducted.[44] LBR was reported only in two trials and analytical pooling showed no significant difference [odds ratio (OR): 1.08; 95% confidence interval (CI): 0.83–1.40].[44] Low-dose aspirin did not have any effect in poor responders[45] and in recipients of donated oocytes.[46,47] Another RCT which looked at combination adjuvant therapy with low-dose aspirin and prednisolone concluded that it does not improve uterine blood flow, implantation, and pregnancy rates.[48] They concluded that low doses of acetylsalicylic acid (ASA) and prednisolone are able to improve ovarian responsiveness to gonadotropins in good-prognosis IVF patients, but do not significantly improve uterine blood flow and pregnancy and implantation rates.[48] They also concluded that this combination could be effective in preventing the onset of severe ovarian hyperstimulation syndrome (OHSS) in high-responder patients during IVF.[48] Yet another meta-analytical pooling showed primary increase in clinical pregnancy rates, but more data is necessary to resolve the issue.[49] But this study also concluded that at this point, there is no reason to change clinical management and discontinue the use of aspirin.[49]
- *L-arginine*: Enhanced vascularization appears to be important for follicular selection and maturation in both spontaneous and stimulated IVF cycles. Nitric oxide, formed in vivo from L-arginine, may play a key role in follicular maturation and ovulation.

  Oral L-arginine supplementation in normally responding patients increases follicular recruitment and reduces the duration of pure FSH (pFSH) treatment, but might also have detrimental effects on embryo quality and pregnancy rate.[50]
- *Estrogen pretreatment*: Pretreatment with ethinyl estradiol improves the success rate of ovulation induction with exogenous gonadotropins in patients with DOR.[51] But for this threshold of 15 mIU/mL for FSH should be achieved before starting ovarian stimulation.[51]

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- *Colony-stimulating factor*: Prospective study of 30 women, where concomitant administration of colony-stimulating factor-1 (CSF-1) and human menopausal gonadotropin (hMG) improved follicle developments, especially in patients with low serum CSF-1 levels in the early follicular phase.[52] No RCTs still and therefore further large-scale, controlled trials are required to assess the efficacy of CSF-1 as adjuvant therapy for poor responders.
- *Letrozole*: Letrozole cotreatment in a gonadotropin-releasing hormone (GnRH) antagonist protocol in poor responders undergoing ART. Two publications have shown that there is insufficient evidence to recommend use of letrozole (low as well as high dose) as an adjuvant in ART stimulation protocols of poor responder patients.[53,54] One publication by Hakan Yarali[55] has shown the effectiveness of letrozole in an antagonist protocol in poor responders. But he has also suggested that future powerful RCTs delineate the optimum controlled ovarian hyperstimulation (COH) protocol to be used in poor responders.[55]

Adjuvants in Polycystic Ovary Syndrome

It can be used for:

- Treatment of androgen excess—prednisone, methyl-prednisolone, and dexamethasone (DEX).
- Hyperinsulinemia/insulin resistance—metformin, inositol.
- Others—N-acetylcysteine (NAC), melatonin, vitamin D, chromium polynicotinate, and L-methylfolate.
- *Glucocorticoids*: Glucocorticoids have been proposed as a useful adjuvant to both clomiphene citrate (CC) and gonadotropin ovulation induction in women with polycystic ovary syndrome (PCOS) with a therapeutic rationale based on reducing adrenal androgen levels, improving ovulatory function, and reducing resistance to ovulation induction agents.[56,57] Glucocorticoids reduce adrenal androgen production by negative feedback inhibition of adrenocorticotropic hormone production which in turn may reduce total circulating androgen levels by as much as 40%, improving folliculogenesis. While major complications from the adjuvant use of low-dose glucocorticoids are rare, weight gain is a common problem. Other reported side effects include glucose intolerance and osteoporosis. Given possible side effects, their use should remain as a second-line therapy.[56,58]

  Dexamethasone is used to treat patients with PCOS who have either adrenal or mixed adrenal and ovarian hyperandrogenism and is given in the dose of 0.25 mg at night from day 2 to 11 of menstrual cycle when undergoing ovulation induction and is supposed to suppress dehydroepiandrosterone sulfate (DHEAS). Aim is to reduce concentration of DHEAS to <400 μg/dL. A study evaluated the effects of short-course administration of DEX combined with CC in CC-resistant patients with PCOS. Eighty-eight percent of the treatment group and 20% of the control group had evidence of ovulation. 46 (40.5%) pregnancies resulted after the combined use of CC and DEX whereas only five (4.2%) women in the control group conceived.[58]
- *Ketoconazole*: Ketoconazole in the dose of 200 mg/day inhibits the key steroidogenic cytochromes with significant reduction in the levels of androstenedione, total and free testosterone.
- *Metformin*: Metformin belongs to the class of biguanides and is the most common drug used as first-line oral therapy for the treatment of type 2 diabetes. Metformin reduces glucose production in the liver, decreases glucose absorption in the intestine, increases insulin secretion in the pancreas, and increases the peripheral glucose uptake in the adipose tissue and muscle.

  Anovulatory women with PCOS and who are resistant to CC may be prescribed metformin as a second-line treatment as adjuvant therapy to CC and gonadotropin ovulation induction. It may also be used as an adjuvant therapy to reduce the risk of developing OHSS in PCOS women undergoing GnRH agonist long protocol IVF/ICSI.[59] After initial reports of effectiveness of metformin in 2015, it was recommended not to use it as monotherapy or in combination with CC for primary ovulation induction, as it has not been shown to improve LBRs. It was recommended to be used as an off-label manner to help improve menstrual cycle regularity or hyperandrogenism in women with PCOS who cannot tolerate or have contraindications to combined oral contraceptive pills.[60] Later in 2017, the Cochrane review concluded that metformin may increase the LBR among women undergoing ovulation induction with gonadotropins in both IUI and ART cycles. This review also said that there is insufficient evidence to show an effect of metformin on multiple pregnancy rates and adverse events like OHSS.[61]

  In 2017, another Cochrane review[62] looked at the role of insulin sensitizers and concluded that:

  – Metformin alone may be beneficial over placebo for LBR, although the quality of evidence was low
  – Data on metformin versus CC for LBR is inconclusive and limited by lack of evidence
  – Results differed by body mass index (BMI), emphasizing the importance of stratifying results by BMI

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- Clomiphene citrate resulted in improvement in CPR and ovulation as compared to metformin alone in obese women with PCOS
- Combined therapy of metformin and CC versus CC alone resulted in improved ovulation rate and CPR, but it is not known whether this translates into increased LBR
- Women taking metformin alone or with combined therapy have no evidence of increased miscarriages or gastrointestinal side effects.

Although there is no current evidence that metformin is teratogenic, when used widely to treat anovulation, then it is possible that rare effects may be unmasked. Metformin therapy therefore needs to be kept under continuing surveillance and adverse outcomes reported.[62]

- *Inositol*: Inositol is a member of the B-complex family of vitamins, but not an essential vitamin and tends to be deficient in women with PCOS. These decreased levels of inositol along with increased urinary clearance of inositol can result in insulin resistance and hyperinsulinemia.[63] Myoinositol increases insulin sensitivity, decreases insulin resistance, improves glucose utilization, decreases free and total testosterone, and restores menstruation and normal ovulation.[64] Myoinositol plays an important role for the signal pathways of cells, particularly in individuals with PCOS. An improved insulin sensitivity may be observed due to the action of myoinositol in PCOS pathway. Several studies indicate that myoinositol is an effective alternative in the treatment of PCOS with no side effects with a standard dosage.[65] Myoinositol has shown beneficial effects on ovarian function and response to ART in women with PCOS as it induces nuclear and cytoplasmic oocyte maturation and promotes embryo development. There is no data available on its effects on pregnancy rate and LBR. In contrast, D-chiro-inositol appears to exert opposite and detrimental effects on the ovary.[66] Further research on larger patient populations is needed to determine whether inositol supplementation, possibly in combination with other drugs, could improve CPR and LBRs in PCOS women undergoing ART.
- *N-acetylcysteine*: NAC as an adjuvant improves insulin sensitivity, decreases androgen level, prevents follicular cohort atresia, and improves quality of cervical mucus. NAC is a safe and well-tolerated adjuvant to CC for induction of ovulation that can improve the ovulation and pregnancy rates in PCOS patients. It may also have some beneficial impacts on endometrial thickness.[67,68]
- *Melatonin*: Melatonin is a hormone of pineal gland, maintains normal circadian rhythms, and governs release of pituitary gonadotropins. Melatonin receptors have been identified in anterior pituitary and ovary also. It is involved in follicular development, ovulation, oocyte maturation, and luteal function. Melatonin deficiency seems to be involved in pathophysiology of PCOS. Melatonin is also a powerful free radical scavenger and has broad-spectrum antioxidant property and has shown to reverse glucose intolerance. Melatonin is taken up into the follicular fluid from the blood and the reactive oxygen species (ROS) produced within the follicles, especially during the ovulation process, was scavenged by melatonin and reduced oxidative stress involved in oocyte maturation and embryo development with improved fertilization and pregnancy rates.[69,70] Despite the antioxidant action of melatonin as per recent meta-analysis, there is no clarity regarding benefit of adding melatonin in all PCOS women.[69,71]
- *Vitamin D*: Vitamin D is a steroid hormone synthesized in the skin by ultraviolet light. Several studies have indicated that most of the women with PCOS are vitamin D deficient. Vitamin D deficiency may be associated with obesity, insulin resistance, and metabolic syndrome, all of which are commonly observed in PCOS and ovulatory dysfunction. In women with PCOS, vitamin D can improve menstrual irregularity, follicular development, and pregnancy rate.[72]
- *Chromium polynicotinate*: Chromium polynicotinate consists of pure niacin-bound chromium binds to niacin and provides a biologically active form of chromium and makes it easier for the body to absorb active component of glucose tolerance factor which is responsible for binding insulin to cell membrane receptor sites, improves insulin sensitivity, and stimulates the metabolism of sugar, fat, and cholesterol. Its deficiency may result in insulin resistance and evidence from clinical studies suggests that low levels of chromium may disrupt glucose and insulin regulation. It is used as an adjuvant therapy for the treatment of anovulation in infertile patients with PCOS.[73]
- *L-methylfolate*: L-methylfolate is a natural, active form of folic acid used at the cellular level for DNA reproduction and the regulation of homocysteine. It reduces homocysteine levels and prevents cardiovascular risk factors associated with PCOS. L-methylfolate, an unmethylated form of folic acid (vitamin B9), is a synthetic form of folate found in nutritional supplements.
- *Coenzyme Q10 (CoQ10)*: CoQ10 seems to be a promising adjuvant to oral ovulatory agents such as CC. It is effective, inexpensive, and safe for stimulating follicular development in CC-resistant PCOS and can be tried successfully before a more complicated treatment such as gonadotropins and laparoscopic ovarian drilling.[74]

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Adjuvants that Reduce the Incidence of Ovarian Hyperstimulation Syndrome

Adjuvants that reduce the incidence of OHSS are described in **Table 2**.

Adjuvants Used to Optimize Assisted Reproductive Technology Outcome

- *Immunoglobulins*: The mode of action is far from being fully understood. It may be of use in improving ART outcome in women with raised peripheral natural killer (NK) cells, positive antithyroid antibodies, positive antiphospholipid antibodies, and shared human leukocyte antigens. But studies have shown that intravenous immunoglobulin (IVIg) failed to improve the LBR in couples with repeated unexplained IVF failure.[75] After this, one publication concluded that IVIg treatment significantly increases the LBR in couples with repeated unexplained IVF failure.[76] But one must remember that immunoglobulins can be associated with anaphylaxis, headache, malaise, flushing, fever, nausea, tachycardia, renal failure, aseptic meningitis, thromboembolic events, and hemolytic anemia.[77]
- *Intralipid*: Twenty percent intravenous fat emulsion made up of egg yolks, soya oil, and water are used as a source of fat and calories in parenteral nutrition. It may help to potentiate the immune system and is not expensive and easy to administer. Not used routinely due to lack of evidence.
- *Steroids*: Steroids alter cytokine production, decrease uterine natural killer (uNK) cells, and modulate autoantibodies expression, but no significant difference was seen in the pregnancy rates, LBR, and ongoing pregnancy rate.[78] These findings were limited to the routine use of glucocorticoids and cannot be extrapolated to women with autoantibodies, unexplained infertility, or recurrent implantation failure (RIF).[78]
- *Vasodilators (sildenafil citrate)*: In a quasi-randomized trial, IVF patients failing to attain an embryo transfer (ET) ≥8 mm were administered sildenafil. It was observed that neither endometrial thickness nor blood supply improved after sildenafil therapy.[79]
- *Aspirin*: Administration of aspirin induces a shift from thromboxane A2 to prostacyclin, leading to vasodilatation and increased peripheral blood supply. Aspirin and heparin are beneficial for women with recurrent miscarriage and antiphospholipid (APL) syndrome.[80,81] RCTs to determine the effect of low-dose aspirin versus placebo or no treatment on the likelihood of clinical outcomes in IVF/ICSI cycles with CPR as the primary outcome did not show any statistical difference. Of these RCTs, LBR was reported only in two trials and analytical pooling showed again no significant difference (OR: 1.08; 95% CI: 0.83–1.40).[44] There was another systemic analysis and meta-analysis published in Fertility and Sterility, which also did not support the use of aspirin in IVF or ICSI treatment on the basis of available evidence does not support. They suggested a definitive trial to show improvement in CPRs.[47]
- *Heparin*: Coagulation disorders could interfere with the different stages of embryo implantation.[82] There is a definite benefit of using heparin in patients with recurrent pregnancy failure related to antiphospholipid antibodies (APS) or other thrombophilic disorders.[83] Use of such antithrombolytic therapies in patients with RIF and without thrombophilic disorders is still debatable

TABLE 2: Adjuvants to reduce the incidence of OHSS.

Drugs	*Effect*	*Evidence*
Cabergoline	Reduces the effects of VEGF-mediated vascular permeability without compromising IR and PR	Grade A
IV calcium infusion (10 mL of 10% calcium gluconate in 200 mL normal saline)	• On the day of oocyte retrieval and days 1, 2, and 3 after oocyte retrieval can decrease OHSS risk • Increased calcium is postulated to inhibit cAMP-stimulated renin secretion, which decreases angiotensin II synthesis and its subsequent effect on VEGF production	Grade B
Prophylactic albumin administration at OR	Clear benefit from IV albumin at OR by increasing the intravascular osmotic pressure thus preventing occurrence of severe OHSS in high-risk cases (OR: 0.28; 95% CI: 0.11–0.73)	Grade C
Hydroxyethyl starch (HAES)	Significantly increases intravascular volume, therefore raising osmotic pressure. It also inhibits platelet aggregation with beneficial effect in decreasing OHSS	GPP
Immunoglobulin	Severe OHSS is associated with low IgG, IgA gamma globulins and therefore administration of IV gamma globulins reduces the severity	No evidence
Corticosteroids	100 mg IV hydrocortisone after OR and followed orally by methylprednisolone effectively reduces the incidence of severe OHSS	No evidence

(cAMP: cyclic adenosine monophosphate; CI: confidence interval; IgA: immunoglobulin A; IgG: immunoglobulin G; IV: intravenous; OHSS: ovarian hyperstimulation syndrome; OR: odds ratio; VEGF: vascular endothelial growth factor)

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as no significant effect on increase in implantation and the rate of live birth was observed.[84-89]

- *Antioxidants and micronutrients*: Supplementing diets with mitochondrial nutrients such as CoQ10 and r-alpha-lipoic acid may potentially be beneficial. We are aware that increased oxidative stress can result in altered glucose metabolism, decreased antiglycation defenses, increased mitochondrial dysfunction, and progressive metabolic impairment.

  Substantial evidence has indicated that some physiological processes, from oocyte maturation to fertilization and embryo development, are particularly sensitive to oxidative stress (OS). These processes require antioxidants for balanced function. The additional treatment with micronutrients, starting 3 months before IVF cycles, protects the follicular microenvironment from oxidative stress, thus increasing the number of good quality oocytes recovered at the pickup.[90,91]

Nonpharmacological Adjuvants

- *Acupuncture*: Used in China for centuries to regulate the female reproductive system. Recent popularity in the Western world. There are three potential mechanisms, which increase neurotransmitters, FSH, estradiol, and uterine blood flow. In traditional acupuncture, the needles were inserted in classical meridian points, or contemporary acupuncture in which the needles were inserted in non-meridian or trigger points.
  Figure 1 shows the acupuncture points.
  Acupuncture can be done during ovarian stimulation, at oocyte recovery, before and after ET. Few systemic reviews and meta-analysis have been conducted on its effectiveness as an adjunct treatment and it is not recommended as a routine use procedure.[92]
- *Acupressure*: In acupressure, stimulation of certain points of the body balances the flow of vital energy. Kovárová et al.[93] observed a significant increase in women's self-efficacy after four sessions of treatment with acupuncture. On the other hand, Cheong et al.[94] did not observe any evidence of overall benefit of acupuncture on improving the LBR.
  Figure 2 illustrates the acupressure points.
- *Massage therapy* prior to ET improves implantation, most likely due to reduction in stress as a result of relaxation effect, reduction in uterine contractions, and an enhancement of blood flow in the abdominal region was also noted (Okhowat J et al., 2015).[95]
- *Complementary and alternative medicines (CAMs)—Reiki and Hypnosis*: CAMs are sometimes used to improve the outcomes of fertility treatment and/or mental health during fertility treatment. Overall, the quality of the evidence across CAM methods was poor because of improper research designs. There is a need for RCTs to determine the effectiveness of CAM in relation to fertility treatment.[96]

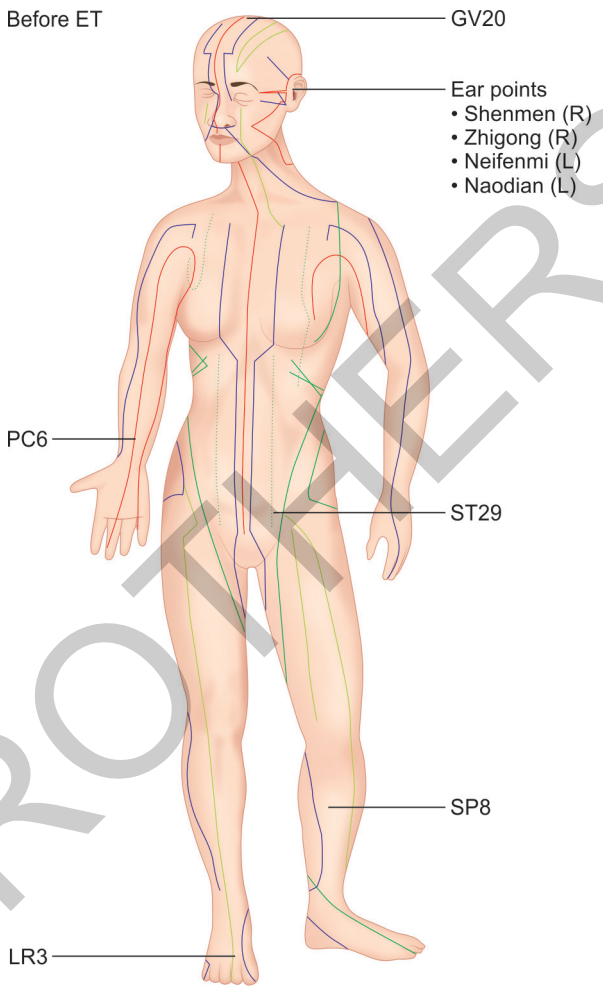

Fig. 1: Acupuncture points for fertility.
(ET: embryo transfer)
Source: Acupuncture Moxibustion. (2019). Acupuncture Moxibustion: Traditional East Asian Therapies. [online] Available from www.acupuncturemoxibustion.com. [Last accessed March, 2020].

Surgery as an Adjuvant to Optimize In Vitro Fertilization Outcome

Routine Hysteroscopy

There is no role in routine hysteroscopy before IVF. It is required in presence of an:

- Abnormal hysterosalpingography (HSG)
- History or symptoms suggestive of endometrial or uterine pathology.

Initial studies showed benefit from pre-IVF hysteroscopy in absence of intrauterine pathology by increasing the chance of pregnancy and the number needed to treat was

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6 [pooled relative risk (RR) = 1.75; 95% CI: 1.51–2.03; P < 0.00001].[97,98]

But the InSIGHT (Intervention Nurses Start Infants Growing on Healthy Trajectories) and TROPHY trials did not show any benefit of routine hysteroscopy prior to first IVF or in women with RIF.[99-101] There was another systematic review and meta-analysis which concluded that from the present data available, no firm conclusions can be made of the effect of diagnostic or operative hysteroscopy on pregnancy outcomes. It was observed that hysteroscopy or no hysteroscopy prior to any (first or subsequent) IVF/ICSI attempt in infertile women without intrauterine abnormalities does not improve LBR.[101] Comparing operative hysteroscopy for intrauterine abnormalities in infertile women with already diagnosed polyps or fibroids, there was low-quality evidence that operative hysteroscopy increases pregnancy rate (RR: 2.13; 95% CI: 1.56–2.92).[102]

The **Figures 3 and 4** highlight different surgical procedures in infertility management that have evidence and those that do not have evidence.

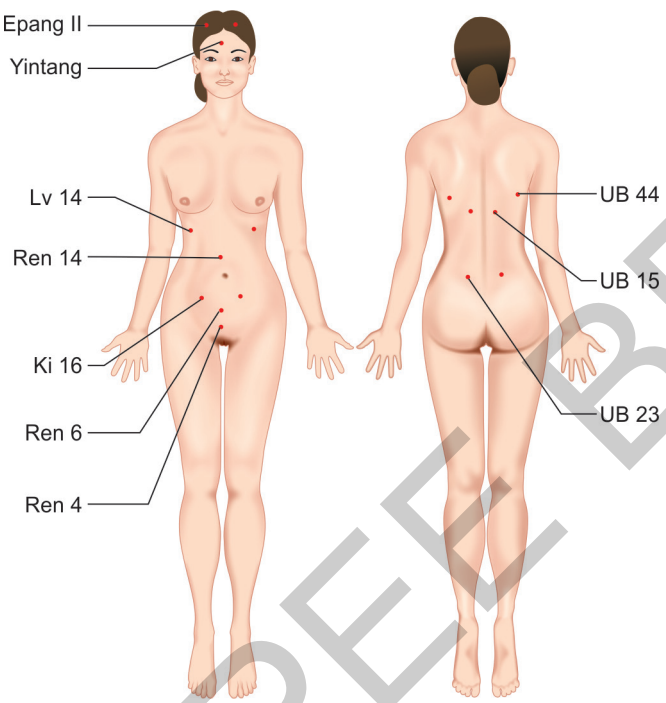


Fig. 2: Acupressure points for fertility.

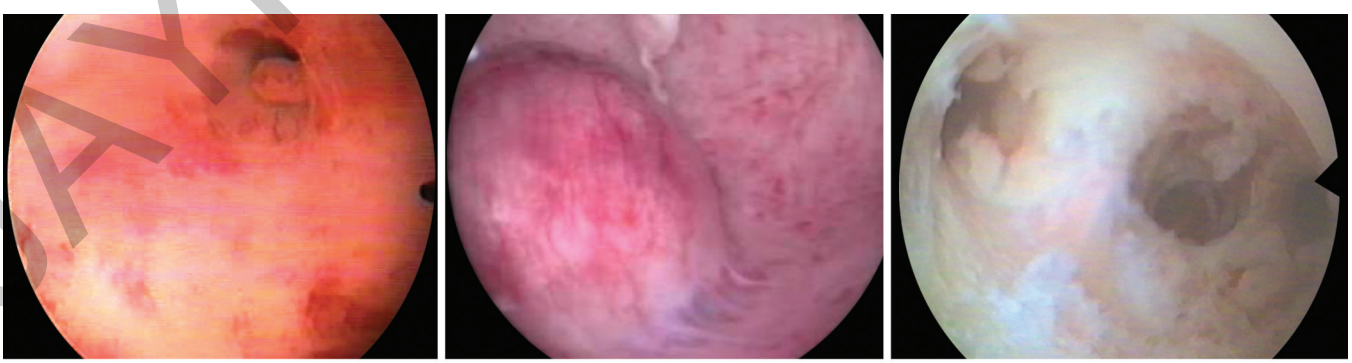
New Technologies Used in Assisted Reproductive Technology

After 40 years of IVF treatment and research, major progress in improving stimulation protocols and fertilization procedures, optimizing embryo culture conditions, and preventing premature luteinization, however only marginal improvement has been seen in the implantation and pregnancy rates. Variability in patient characteristics and response to ART dictate the need for proven, personalized diagnostic and therapeutic approaches to optimize efficacy and safety outcomes**.** Different methods of selection of gametes and embryos have been used to improve the IVF outcome **(Fig. 5)**.

Of these, spindle view and intracytoplasmic morphologically selected sperm injection (IMSI) have shown no benefit. There is some evidence for the use of physiological intracytoplasmic sperm injection (PICSI).

Blastocyst Transfer

The scientific rationale for blastocyst transfer is to increase implantation rates by improving uterine and embryonic synchronicity and allowing self-selection of embryos with greater implantation potential, but greater standardization of blastocyst morphology scales is required for this.[103-105] Though the embryo-endometrial synchrony is present with blastocyst transfer, with a higher implantation and LBR, it has a higher ET cancelation rate[106,107] with fewer embryos cryopreserved.[107,108]



Polyp | Submucous myoma | Intrauterine adhesion

Fig. 3: Reproductive surgery indicated beyond a reasonable doubt.

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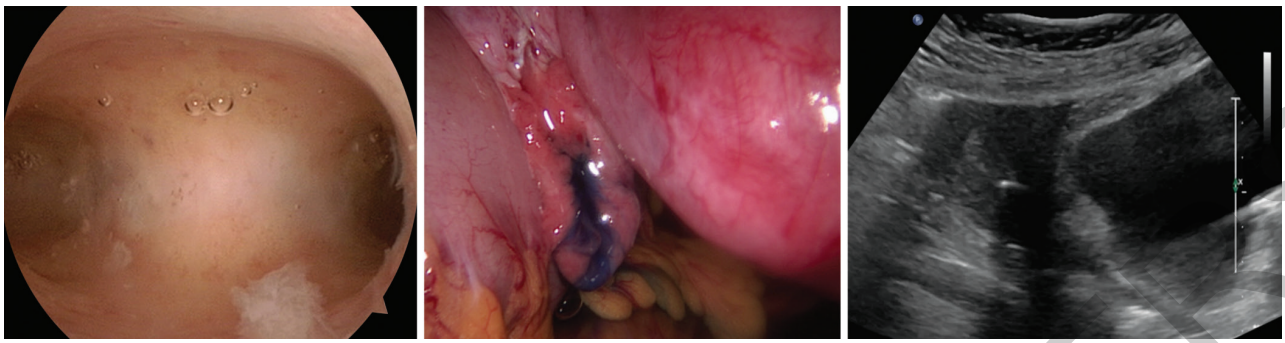

Fig. 4: Routine hysteroscopy laparoscopy and endometrial scratch.

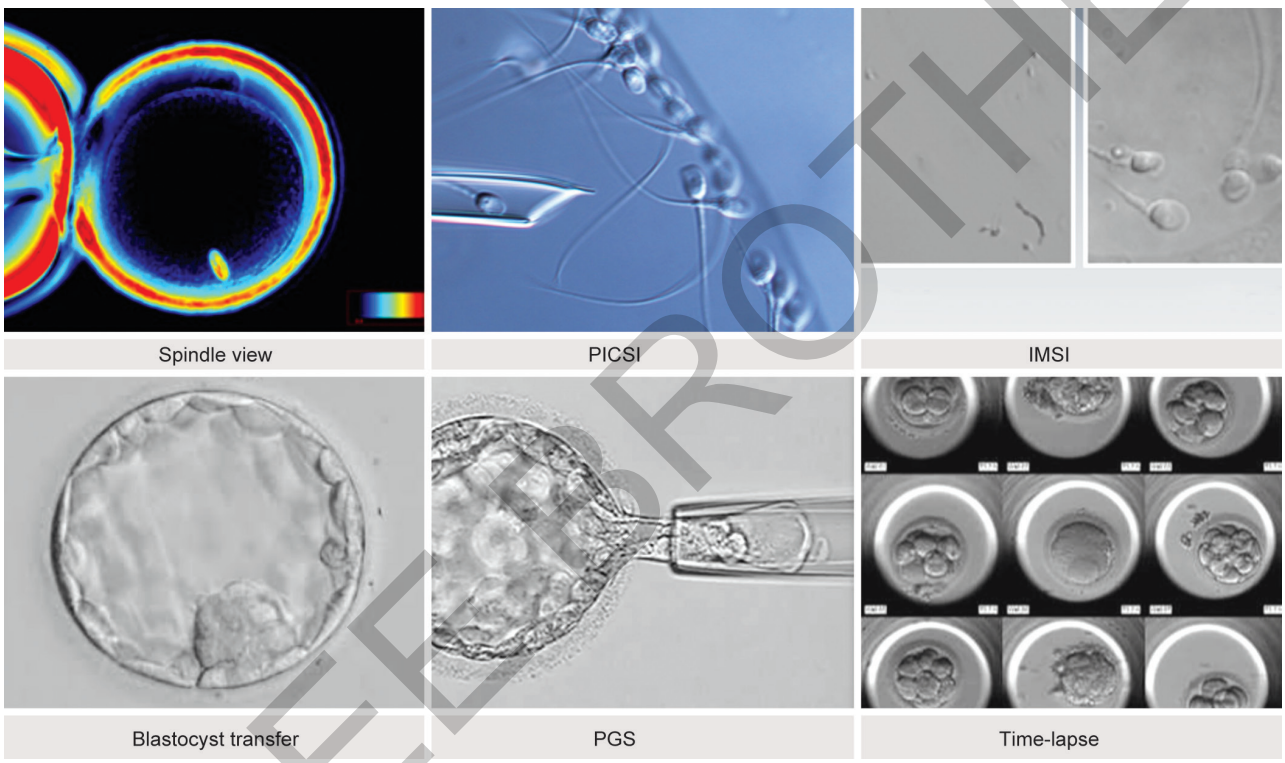

Fig. 5: Techniques used in the laboratory to improve ART outcome.
(ART: assisted reproductive technology; IMSI: intracytoplasmic morphologically selected sperm injection; PGS: preimplantation genetic screening; PICSI: physiological intracytoplasmic sperm injection)

Time-lapse

Time-lapse is a noninvasive embryo assessment of morphokinetic parameters. Though time-lapse is a perfect tool for studying and understanding early embryo cleavages as it gives detailed information with flexibility in workflow having controlled incubation conditions and being precise, it has not yet been validated in large studies. Embryos cultured in constant and uninterrupted conditions[109] with detection of irregularities in cell cleavages which can then be deselected for ET enhancing clinical reproductive outcome.[110]

There is insufficient good-quality evidence of differences in live birth or ongoing pregnancy, miscarriage and stillbirth, or clinical pregnancy to choose between time-lapse, with or without embryo selection software, and conventional incubation.[111] Moreover, embryo culture and light exposure safety need to be evaluated and processing abundant imaging data in real-time is a challenge and is not done in most laboratories. It is also a poor predictor of IVF outcome as too many confounding factors influence the dynamics of embryo development.

Embryo Biopsy + Preimplantation Genetic Testing for Aneuploidy

Preimplantation genetic testing for aneuploidy (PGT-A) may be done to increase clinical outcomes, decrease loss rates, and decrease transfer order in IVF by transfer of

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euploid embryos. One must remember that PGT-A does not improve embryo quality or increase LBR. Fluorescence in situ hybridization (FISH) and day 3 biopsy have a negative impact on development and outcome of IVF with no increase in chances of having a baby.[112] The value of PGT-A as a universal screening test for all IVF patients has yet to be determined. The chances of false-positive testing, embryonic damage, and loss of euploid embryos are high, especially due to mosaicism. Other important considerations about PGT-A that must be addressed by further research include cost-effectiveness; the role and effect of cryopreservation, time to pregnancy, utility in specific subgroups (such as recurrent loss, prior implantation failure, advanced maternal age, etc.); cumulative success rates over time; and total reproductive potential per intervention.[113]

KEY MESSAGES

- Insufficient evidence to identify the use of any one particular intervention in the management of poor responders in IVF to improve treatment outcomes either for:
  - Pituitary downregulation
  - Ovarian stimulation
  - Adjuvant therapy.
- There is a need to identify those subgroups of poor responders that have theca cell failure but retain a relatively preserved GC function, as modulating their intrafollicular androgen environment by exogenous androgens may improve their ovarian response.
- Patients for whom other modalities of treatment have failed may consider the option of androgen administration.
- Management of poor responders and women with low ovarian reserve still represents a challenge for the clinician.
- Use of adjuvants in PCOS is empirical, though recent publications have shown metformin to increase pregnancy rate in gonadotropin cycles.
- Adjuvant therapy may be beneficial in preventing or reducing the severity of OHSS.
- Current evidence for adjuvants in routine IVF is still weak.
- At present, however, there is insufficient evidence to recommend the routine use of blastocyst biopsy with aneuploidy testing in all infertile patients.
- When unproven therapeutic approaches are prescribed, patients should be made aware of the lack of evidence for clinical benefits and the potential of treatment.
- Currently, little good-quality evidence to support the use of specific ART-related laboratory procedures—ICSI for all, blastocyst transfer, assisted hatching, time-lapse imaging, and freeze all.
- Evaluating the failed IVF cycle often provides useful prognostic information.
- Good medical practice dictates that the physician keeps the best interest of their patients in mind and counsel patients appropriately about the best evidence available and potential adverse effects of the treatments prescribed.
- Adaptation and personalization of fertility therapy may help to optimize efficacy and safety outcomes for individual.
- Prognostic modeling and personalized management strategies based on individual patient characteristics may prove to represent real progress toward improved treatment.
- Greater quality control and standardization of clinical and laboratory evaluations optimize ART practice and improves individual patient outcomes.

REFERENCES

1. Macklon NS, Geraedts JP, Fauser BC. Conception to ongoing pregnancy: the 'black box' of early pregnancy loss. Hum Reprod Update. 2002;8:333-43.
2. Lanzone A, Di Simone N, Castellani R, et al. Human growth hormone enhances progesterone production by human luteal cells in vitro: evidence of a synergistic effect with human chorionic gonadotropin. Fertil Steril. 1992;57:92-6.
3. Harper K, Proctor M, Hughes E. Growth hormone for in vitro fertilization. Cochrane Database Syst Rev. 2003;3:CD000099.
4. Kolibianakis EM, Venetis CA, Diedrich K, et al. Addition of growth hormone to gonadotrophins in ovarian stimulation of poor responders treated by in-vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update. 2009;15:613-22.
5. Duffy JM, Ahmad G, Mohiyiddeen L, et al. Growth hormone for in vitro fertilization. Cochrane Database Syst Rev. 2010;1:CD000099.
6. Li XL, Wang L, Lv F, et al. The influence of different growth hormone addition protocols to poor ovarian responders on clinical outcomes in controlled ovary stimulation cycles: a systematic review and meta-analysis. Medicine (Baltimore). 2017;96:e6443.
7. Bayoumi YA, Dakhly DR, Bassiouny YA, et al. Addition of growth hormone to the microflare stimulation protocol among women with poor ovarian response. Int J Gynaecol Obstet. 2015;131:305-8.
8. Hart RJ, Rombauts L, Norman RJ. Growth hormone in IVF cycles: any hope? Curr Opin Obstet Gynecol. 2017;29:119-25.
9. Yu X, Ruan J, He LP, et al. Efficacy of growth hormone supplementation with gonadotrophins in vitro fertilization for poor ovarian responders: an updated meta-analysis. Int J Clin Exp Med. 2015;8:4954-67.
10. Norman RJ, Alvino H, Hull LM, et al. Human growth hormone for poor responders: a randomized placebo-controlled trial provides no evidence for improved live birth rate. Reprod Biomed Online. 2019;38:908-15.
11. Doldi N, Bassan M, Bonzi V, et al. Effects of growth hormone and growth hormone-releasing hormone on steroid synthesis in cultured human luteinizing granulosa cells. Gynecol Endocrinol. 1996;10:101-8.

JAYPEE BROTHERS

12. Howles CM, Loumaye E, Germond M, et al. Does growth hormone-releasing factor assist follicular development in poor responder patients undergoing ovarian stimulation for in-vitro fertilization? Hum Reprod. 1999;14:1939-43.
13. Delitala G, Tomasi P, Virdis R. Neuroendocrine regulation of human growth hormone secretion. Diagnostic and clinical applications. J Endocrinol Invest. 1988;11:441-62.
14. Kim CH, Chae HD, Chang YS. Pyridostigmine cotreatment for controlled ovarian hyperstimulation in low responders undergoing in vitro fertilization-embryo transfer. Fertil Steril. 1999;71:652-7.
15. Chung-Hoon K, Hee-Dong C, Yoon-Seok C. Pyridostigmine cotreatment for controlled ovarian hyperstimulation in low responders undergoing in vitro fertilization ± embryo transfer. Fertil Steril. 1999;71:652-7.
16. Harlow CR, Hillier SG, Hodges JK. Androgen modulation of follicle-stimulating hormone-induced granulosa cell steroidogenesis in the primate ovary. Endocrinology. 1986;119:1403-5.
17. Hillier SG, De Zwart FA. Evidence that granulosa cell aromatase induction/activation by follicle-stimulating hormone is an androgen receptor-regulated process in-vitro. Endocrinology. 1981;109:1303-5.
18. Weil S, Vendola K, Zhou J, et al. Androgen and follicle-stimulating hormone interactions in primate ovarian follicle development. J Clin Endocrinol Metab. 1999;84:2951-6.
19. Vendola KA, Zhou J, Adesanya OO, et al. Androgens stimulate early stages of follicular growth in the primate ovary. J Clin Invest. 1998;101:2622-9.
20. Casson PR, Lindsay MS, Pisarska MD, et al. Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: a case series. Hum Reprod. 2000;10:2129-32.
21. Balasch J, Fabregues F, Penarrubia J, et al. Pretreatment with transdermal testosterone may improve ovarian response to gonadotrophins in poor-responder IVF patients with normal basal concentrations of FSH. Hum Reprod. 2006;7:1884-93.
22. Bosdou JK, Venetis CA, Kolibianakis EM, et al. The use of androgens or androgen-modulating agents in poor responders undergoing in vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update. 2012;18:127-45.
23. Bosdou JK, Venetis CA, Dafopoulos K, et al. Transdermal testosterone pretreatment in poor responders undergoing ICSI: a randomized clinical trial. Hum Reprod. 2016;31:977-85.
24. Hillier SG, Whitelaw PF, Smyth CD. Follicular oestrogen synthesis: The 'two-cell, two-gonadotrophin' model revisited. Mol Cell Endocrinol. 1994;100:51-4.
25. Barad D, Brill H, Gleicher N. Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian function. J Assist Reprod Genet. 2007;24:629-34.
26. Hyman EJ, Margalioth EJ, Rabinowitz R, et al. Dehydroepiandrosterone (DHEA) supplementation for poor responders-how does it work? Fertil Steril. 2010;94:S86.
27. Mamas L, Mamas E. Premature ovarian failure and dehydroepiandrosterone. Fertil Steril. 2009;91:644-6.
28. Sönmezer M, Cil AP, Oktay K. Ongoing pregnancies from early retrieval of prematurely developing antral follicles after DHEA supplementation. Reprod Biomed Online. 2009;19:816-9.
29. Wiser A, Gonen O, Ghetler Y, et al. Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study. Hum Reprod. 2010;25:2496-500.
30. Narkwichean A, Maalouf W, Campbell BK, et al. Efficacy of dehydroepiandrosterone to improve ovarian response in women with diminished ovarian reserve: a meta-analysis. Reprod Biol Endocrinol. 2013;11:44.
31. Ubaldi F, Vaiarelli A, D'Anna R, et al. Management of poor responders in IVF: is there anything new? Biomed Res Int. 2014;2014:352098.
32. Xu B, Li Z, Yue J, et al. Effect of dehydroepiandrosterone administration in patients with poor ovarian response according to the Bologna criteria. PLoS One. 2014;9:e99858.
33. Gleicher N, Weghofer A, Barad DH. Dehydroepiandrosterone (DHEA) reduces embryo aneuploidy: direct evidence from preimplantation genetic screening (PGS). Reprod Biol Endocrinol. 2010;8:140.
34. Gleicher N, Weghofer A, Barad DH. Discordances between follicle stimulating hormone (FSH) and anti-Müllerian hormone (AMH) in female infertility. Reprod Biol Endocrinol. 2010;8:64.
35. Borman E, Check JH, Williams JM, et al. No evidence to support the concept that low serum dehydroepiandrosterone (DHEA) sulphate (S) levels are associated with less oocyte production or lower pregnancy rates. Clin Exp Obstet Gynecol. 2012;39:429-31.
36. Motta EL, Rossi LM, Fernandes TR, et al. The use of DHEA in poor responders does not improve IVF outcomes: insights of a pilot study. Fertil Steril. 2006;86:S428.
37. Yakin K, Urman B. DHEA as a miracle drug in the treatment of poor responders; hype or hope? Hum Reprod. 2011;26:1941-4.
38. Sönmezer M, Ozmen B, Cil AP, et al. Dehydroepiandrosterone supplementation improves ovarian response and cycle outcome in poor responders. Reprod Biomed Online. 2009;19:508-13.
39. Sciard C, Berthiller J, Brosse A, et al. Preliminary results of DHEA in poor responders in IVF. Open J Obstet Gynecol. 2016;6:396-403.
40. Zhang M, Niu W, Wang Y, et al. Dehydroepiandrosterone treatment in women with poor ovarian response undergoing IVF or ICSI: a systematic review and meta-analysis. J Assist Reprod Genet. 2016;33:981-91.
41. Szymusik I, Marianowski P, Zygula A, et al. Poor responders in IVF—is there any evidence-based treatment for them? Neuro Endocrinol Lett. 2015;36:209-13.
42. González-Comadran M, Durán M, Solà I, et al. Effects of transdermal testosterone in poor responders undergoing IVF: systematic review and meta-analysis. Reprod Biomed Online. 2012;25:450-9.
43. Polyzos NP, Davis SR, Drakopoulos P, et al. Testosterone for poor ovarian responders: lessons from ovarian physiology. Reprod Sci. 2016;25:980-2.
44. Gelbaya TA, Kyrgiou M, Li TC, et al. Low-dose aspirin for in vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update. 2007;13:357-64.
45. Lok IH, Yip SK, Cheung LP, et al. Adjuvant low-dose aspirin therapy in poor responders undergoing in vitro fertilization: a prospective, randomized, double-blind, placebo-controlled trial. Fertil Steril. 2004;81:556-61.
46. Weckstein LN, Jacobson A, Galen D, et al. Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective, randomized study. Fertil Steril. 1997;68:927-30.
47. Khairy M, Banerjee K, El-Toukhy T, et al. Aspirin in women undergoing in vitro fertilization treatment: a systematic review and meta-analysis. Fertil Steril. 2007;88:822-31.
48. Revelli A, Dolfin E, Gennarelli G, et al. Low-dose acetylsalicylic acid plus prednisolone as an adjuvant treatment in IVF: a prospective, randomized study. Fertil Steril. 2008;90:1685-91.
49. Ruopp MD, Collins TC, Whitcomb BW, et al. Evidence of absence or absence of evidence? A reanalysis of the effects of low-dose aspirin in in vitro fertilization. Fertil Steril. 2008;90:71-6.
50. Battaglia C, Regnani G, Marsella T, et al. Adjuvant L-arginine treatment in controlled ovarian hyperstimulation: a double-blind, randomized study. Hum Reprod. 2002;17:659-65.
51. Tartagni M, Cicinelli E, De Pergola G, et al. Effects of pretreatment with estrogens on ovarian stimulation with gonadotropins in

JAYPEE BROTHERS

women with premature ovarian failure: a randomized, placebo-controlled trial. Fertil Steril. 2007;87:858-61.
52. Takasaki A, Ohba T, Okamura Y, et al. Clinical use of colony-stimulating factor-1 in ovulation induction for poor responders. Fertil Steril. 2008;90:2287-90.
53. Ebrahimi M, Akbari-Asbagh F, Ghalandar-Attar M. Letrozole + GnRH antagonist stimulation protocol in poor ovarian responders undergoing intracytoplasmic sperm injection cycles: An RCT. Int J Reprod Biomed (Yazd). 2017;15:101-8.
54. Fouda UM, Sayed AM. Extended high dose letrozole regimen versus short low dose letrozole regimen as an adjuvant to gonadotropin releasing hormone antagonist protocol in poor responders undergoing IVF-ET. Gynecol Endocrinol. 2011;27:1018-22.
55. Yarali H, Esinler İ, Polat M, et al. Antagonist/letrozole protocol in poor ovarian responders for intracytoplasmic sperm injection: a comparative study with the microdose flare-up protocol. Fertil Steril. 2009;92:231-5.
56. Begum MR, Ehsan M, Begum MS, et al. Beneficial effects of addition of glucocorticoid during induction of ovulation by letrozole in polycystic ovarian syndrome. J South Asian Fed Obstet Gynaecol. 2012;4:85-9.
57. Macklon N, Fauser BC. Medical approaches to ovarian stimulation for infertility. Reprod Endocrinol. 2009;2:689-724.
58. Parsanezhad M, Alborzi S, Motazedian S, et al. Use of dexamethasone and clomiphene citrate in the treatment of clomiphene citrate-resistant patients with polycystic ovary syndrome and normal dehydroepiandrosterone sulfate levels: a prospective, double-blind, placebo-controlled trial. Fertil Steril. 2002;78:1001-4.
59. Tso LO, Costello MF, Albuquerque LE, et al. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2014;11:CD006105.
60. Usadi RS, Merriam KS. On-label and off-label drug use in the treatment of female infertility. Fertil Steril. 2015;103:583-94.
61. Bordewijk EM, Nahuis M, Costello MF, et al. Metformin during ovulation induction with gonadotrophins followed by timed intercourse or intrauterine insemination for subfertility associated with polycystic ovary syndrome. Cochrane Database Syst Rev. 2017;1:CD009090.
62. Morley LC, Tang T, Yasmin E, et al. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2017;11:CD003053.
63. Baillargeon JP, Diamanti-Kandarakis E, Ostlund RE, et al. Altered D-chiro-inositol urinary clearance in women with polycystic ovary syndrome. Diabetes Care. 2006;29:300-5.
64. Unfer V, Carlomagno G, Dante G, et al. Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials. Gynecol Endocrinol. 2012;28:509-15.
65. Regidor PA, Schindler AE. Myoinositol as a safe and alternative approach in the treatment of infertile PCOS women: a German observational study. Int J Endocrinol. 2016;2016:9537632.
66. Garg D, Tal R. Inositol treatment and ART outcomes in women with PCOS. Int J Endocrinol. 2016;2016:1979654.
67. Salehpour S, Sene AA, Saharkhiz N, et al. N-acetylcysteine as an adjuvant to clomiphene citrate for successful induction of ovulation in infertile patients with polycystic ovary syndrome. J Obstet Gynaecol Res. 2012;38:1182-6.
68. Maged AM, Elsawah H, Abdelhafez A, et al. The adjuvant effect of metformin and N-acetylcysteine to clomiphene citrate in induction of ovulation in patients with polycystic ovary syndrome. Gynecol Endocrinol. 2015;31:635-8.
69. Basheer M, Rai S, Hsu TC. Melatonin vs. phytomelatonin: therapeutic uses with special reference to polycystic ovarian syndrome (PCOS). Cogent Biol. 2016;2:1136257.
70. Fernando S, Rombauts L. Melatonin: shedding light on infertility?—a review of the recent literature. J Ovarian Res. 2014;7:98.
71. Seko LM, Moroni RM, Leitao VM, et al. Melatonin supplementation during controlled ovarian stimulation for women undergoing assisted reproductive technology: systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2014;101:154-61.e4.
72. Irani M, Merhi Z. Role of vitamin D in ovarian physiology and its implication in reproduction: a systemic review. Fertil Steril. 2014;102:460-8.e3.
73. Deshpande H. Practical Management of Ovulation Induction. New Delhi: Jaypee Brothers Medical Publishers (P) Pvt. Ltd.; 2016.
74. El-Refaeey A, Selem A, Badawy A. Combined coenzyme Q10 and clomiphene citrate for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome. Reprod Biomed Online. 2014;29:119-24.
75. Stephenson MD, Fluker MR. Treatment of repeated unexplained in vitro fertilization failure with intravenous immunoglobulin: a randomized, placebo-controlled Canadian trial. Fertil Steril. 2000;74:1108-13.
76. Clark DA, Coulam CB, Stricker RB. Is intravenous immunoglobulins (IVIG) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF). J Assist Reprod Genet. 2006;23:1-3.
77. Sherer Y, Levy Y, Langevitz P, et al. Adverse effects of intravenous immunoglobulin therapy in 56 patients with autoimmune diseases. Pharmacology. 2001;62:133-7.
78. Boomsma CM, Keay SD, Macklon NS. Peri-implantation glucocorticoid administration for assisted reproductive technology cycles. Cochrane Database Syst Rev. 2012;6:CD005996.
79. Check JH, Graziano V, Lee G, et al. Neither sildenafil nor vaginal estradiol improves endometrial thickness in women with thin endometrial after taking oral estradiol in graduating dosages. Clin Exp Obstet Gynecol. 2004;31:99-102.
80. Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol. 1996;174:1584-9.
81. Tulppala M, Marttunen M, Söderstrom-Anttila V, et al. Low-dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. Hum Reprod. 1997;12:1567-72.
82. Stern C, Chamley L, Hale L, et al. Antibodies to β2 glycoprotein I are associated with in vitro fertilization implantation failure as well as recurrent miscarriage: results of a prevalence study. Fertil Steril. 1998;70:938-44.
83. Urman B, Ata B, Yakin K, et al. Luteal phase empirical low molecular weight heparin administration in patients with failed ICSI embryo transfer cycles: a randomized open-labeled pilot trial. Hum Reprod. 2009;24:1640-7.
84. Akhtar MA, Eljabu H, Hopkisson J, et al. Aspirin and heparin as adjuvants during IVF do not improve live birth rates in unexplained implantation failure. Reprod Biomed Online. 2013;26:586-94.
85. Noci I, Milanini MN, Ruggiero M, et al. Effect of dalteparin sodium administration on IVF outcome in non-thrombophilic young women: a pilot study. Reprod Biomed Online. 2011;22:615-20.

JAYPEE BROTHERS

86. Stern C, Chamley L, Norris H, et al. A randomized, double-blind, placebo-controlled trial of heparin and aspirin for women with in vitro fertilization implantation failure and antiphospholipid or antinuclear antibodies. Fertil Steril. 2003;80:376-83.
87. Sher G, Feinman M, Zouves C, et al. High fecundity rates following in-vitro fertilization and embryo transfer in antiphospholipid antibody seropositive women treated with heparin and aspirin. Hum Reprod. 1994;9:2278-83.
88. Simon A, Laufer N. Assessment and treatment of repeated implantation failure (RIF). J Assist Reprod Genet. 2012;29: 1227-39.
89. Hamdi K, Danaii S, Farzadi L, et al. The role of heparin in embryo implantation in women with recurrent implantation failure in the cycles of assisted reproductive techniques (without history of thrombophilia). J Family Reprod Health. 2015;9:59-64.
90. Luddi A, Capaldo A, Focarelli R, et al. Antioxidants reduce oxidative stress in follicular fluid of aged women undergoing IVF. Reprod Biol Endocrinol. 2016;14:57.
91. Wang S, He G, Chen M, et al. The role of antioxidant enzymes in the ovaries. Oxid Med Cell Long. 2017;2017:4371714.
92. Cheong YC, Ng EH, Ledger WL. Acupuncture and assisted conception. Cochrane Database Syst Rev. 2008;4:CD006920.
93. Kovárová P, Smith CA, Turnbull DA. An exploratory study of the effect of acupuncture on self-efficacy for women seeking fertility support. Explore (NY). 2010;6:330-4.
94. Cheong KB, Zhang JP, Huang Y, et al. The effectiveness of acupuncture in prevention and treatment of postoperative nausea and vomiting—a systematic review and meta-analysis. PLoS One. 2013;8:e82474.
95. Okhowat J, Murtinger M, Schuff M, et al. Massage therapy improves in vitro fertilization outcome in patients undergoing blastocyst transfer in a cryo-cyde. Alternative Therapies in Health & Medicine. 2015;21(2).
96. Miner SA, Robins S, Zhu YJ, et al. Evidence for the use of complementary and alternative medicines during fertility treatment: a scoping review. BMC Complement Altern Med. 2018;18:158.
97. El-Toukhy T, Sunkara SK, Coomarasamy A, et al. Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and meta-analysis. Reprod Biomed Online. 2008;16:712-9.
98. Bosteels J, Weyers S, Puttemans P, et al. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Hum Reprod Update. 2010;16:1-11.
99. Smit JG, Kasius JC, Eijkemans MJ, et al. The inSIGHT study: costs and effects of routine hysteroscopy prior to a first IVF treatment cycle. A randomised controlled trial. BMC Womens Health. 2012;12:22.
100. Smit JG, Kasius JC, Eijkemans MJ, et al. Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial. Lancet. 2016;387:2622-9.
101. El-Toukhy T, Campo R, Khalaf Y, et al. Hysteroscopy in recurrent in-vitro fertilisation failure (TROPHY): a multicentre, randomised controlled trial. Lancet. 2016;387:2614-21.
102. Di Spiezio Sardo A, Di Carlo C, Minozzi S, et al. Efficacy of hysteroscopy in improving reproductive outcomes of infertile couples: a systematic review and meta-analysis. Hum Reprod Update. 2016;22:479-96.
103. Wilson M, Hartke K, Kiehl M, et al. Integration of blastocyst transfer for all patients. Fertil Steril. 2002;77:693-6.
104. Blake DA, Farquhar CM, Johnson N, et al. Cleavage stage versus blastocyst stage embryo transfer in assisted conception. Cochrane Database Syst Rev. 2007;17:CD002118.
105. Montag M, Toth B, Strowitzki T. New approaches to embryo selection. Reprod Biomed Online. 2013;27:539-46.
106. Marek D, Langley M, Gardner DK, et al. Introduction of blastocyst culture and transfer for all patients in an in vitro fertilization program. Fertil Steril. 1999;72:1035-40.
107. Papanikolaou EG, D'haeseleer E, Verheyen G, et al. Live birth rate is significantly higher after blastocyst transfer than after cleavage-stage embryo transfer when at least four embryos are available on day 3 of embryo culture. A randomized prospective study. Hum Reprod. 2005;20:3198-203.
108. Tsirigotis M. Blastocyst stage transfer: pitfalls and benefits. Too soon to abandon current practice? Hum Reprod. 2008;13:3285-9.
109. Ciray HN, Campbell A, Agerholm IE, et al. Proposed guidelines on the nomenclature and annotation of dynamic human embryo monitoring by a time-lapse user group. Hum Reprod. 2014;29:2650-60.
110. Hojnik N, Vlaisavljević V, Kovačič B. Morphokinetic characteristics and developmental potential of in vitro cultured embryos from natural cycles in patients with poor ovarian response. Biomed Res Int. 2016;2016:4286528.
111. Armstrong S, Bhide P, Jordan V, et al. Time-lapse systems for embryo incubation and assessment in assisted reproduction. Cochrane Database Syst Rev. 2018;5:CD011320.
112. Twisk M, Mastenbroek S, Hoek A, et al. No beneficial effect of preimplantation genetic screening in women of advanced maternal age with a high risk for embryonic aneuploidy. Hum Reprod. 2008;23:2813-7.
113. Penzias A, Bendikson K, Butts S, et al. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril. 2018;109:429-36.

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FOGSI Focus Use of Adjuvants in INFERTILITY

Assisted human reproduction continues its worldwide spread as increasing numbers of patients are treated annually, and more clinicians and scientists enter the field each year. This *FOGSI focus on Use of Adjuvants in Infertility* is a comprehensive text covering all aspects of adjuvant therapy in infertility. Data on adjuvants are presented in 10 detailed chapters, each debating the topic on pros and cons of this form of treatment. The book will no doubt prove invaluable for clinicians dealing with couples facing subfertility as well as for reproductive medicine and infertility fellows and residents, who will find a comprehensive overview for the clinical practices of a fertility clinic.

Sunita Tandulwadkar MD (Obstetrics and Gynecology) FICS (Gyne-Endoscopy) FICOG is currently the President of the Indian Association of Gynaecological Endoscopists (IAGE), the elected second Vice President, Indian Society of Assisted Reproduction (ISAR), the Chairperson and Founder Honorary Secretary of the Maharashtra State Chapter—ISAR (MSR). She is the Head, Department of Obstetrics and Gynecology, Ruby Hall Clinic, Pune, Maharashtra, India; the Chief, Ruby Hall IVF and Endoscopy Center, Pune; and the Director, Solo Clinic, Center of Excellence Infertility and Endoscopy, Pune. She is the Founder and Medical Advisor, Solo Stem Cells, Stem Cells Research and Application Center, Pune. She has also held the prestigious position of Vice President—West Zone of the Federation of Obstetric and Gynaecological Societies of India (FOGSI); and was an elected Board Member of the International Society of Gynecologic Endoscopy (ISGE); Advisor and Reviewer of Journal of Human Reproductive Sciences, Pioneer in Stem Cells in India and has on her record, delivering World's first Baby at age of 45 with rejuvenation of ovary with autologous stem cells. She is a prolific Writer and intuitive Researcher, has authored five of her own books, and has more than 10 publications in peer-reviewed journals. She has been bestowed by several awards such as the Bharat Gaurav Puraskar, Punyashloka Ahilyabai Holkar Award, Best Citizen of India and the Rashtriya Gaurav Award—for her dedicated and pioneering work in her field of expertise.

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