INDIAN FERTILITY SOCIETY

SIG Newsletter

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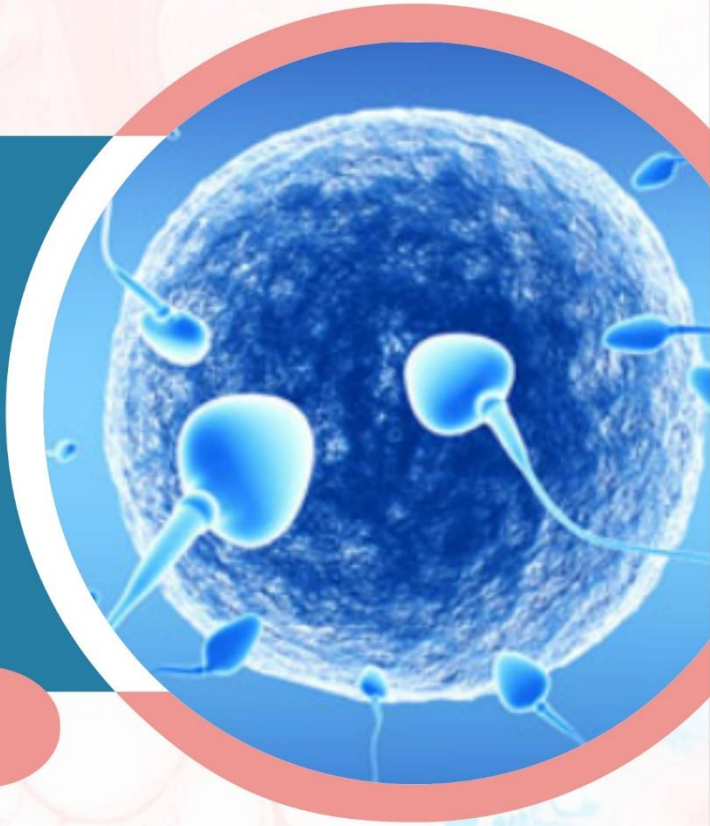

Reproductive Endocrinology

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Enhancing Success Rates: Add-On Strategies for Ovarian Stimulation in Assisted Reproduction

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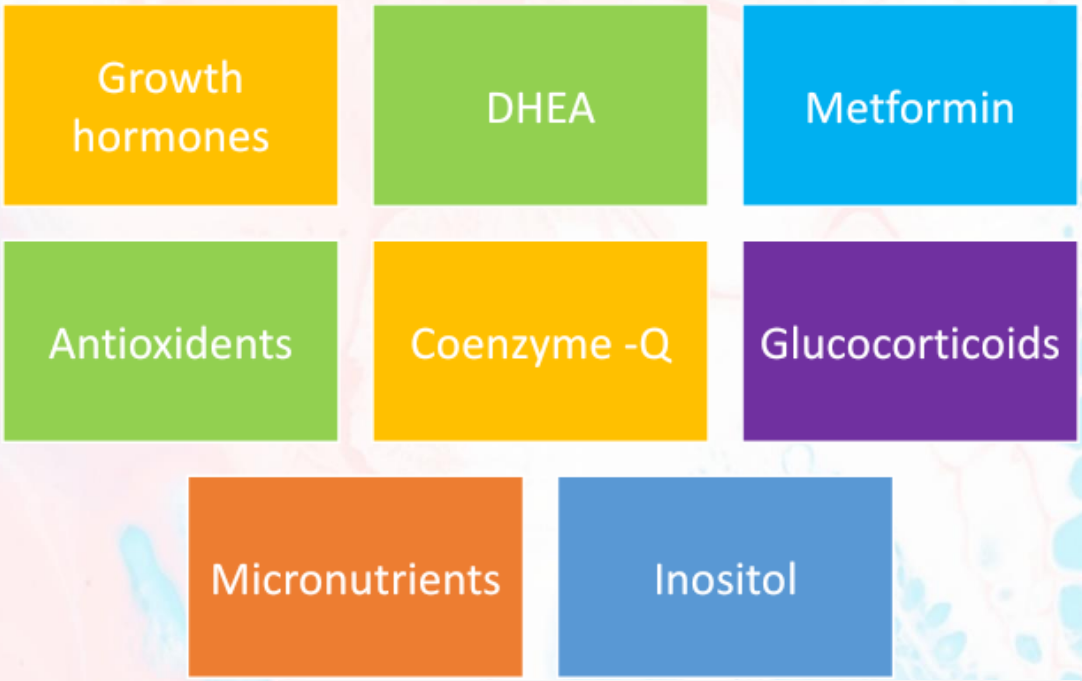
Add on is an additive that enhances the effectiveness of treatment. The earliest known use of the word add-on is in the 1930s, which was derived from Oxford English Dictionary's, US Patent. It is a drug or substance that enhances the efficacy of a primary drug whose mechanisms of actions have been proposed. These drugs have been evaluated in phase 1 and

phase 2 trials of research. Their use is not a routine, only in select patients by clinicians who rely on their experience-based recommendations.

Ovarian stimulation is a critical component of in vitro fertilisation (IVF), designed to increase the number of oocytes available for fertilisation. However, despite advancements in standard stimulation protocols, challenges such as poor ovarian response and suboptimal embryo quality persist. To address these, various add-on strategies have been introduced to enhance oocytes, sperms, embryo quality and in turn enhance success rates. This article explores some of the key add-on interventions used in ovarian stimulation and their potential impact on assisted reproductive techniques such as IUI and IVF success rates.

Add-On therapy is helpful in various condition like PCOS, poor responders and other conditions to improve number and quality of oocytes retrieved.

Figure-1 Add-On for ovarian stimulation in IVF



Growth Hormone: Growth hormone (GH) is a peptide hormone secreted from the pituitary gland in response to growth hormone releasing hormone, and its secretion is inhibited by growth hormone inhibiting hormone (somatostatin) released form the hypothalamus into the hypophyseal portal system surrounding the pituitary gland. Growth hormone enhances the effects on granulosa cells and stimulates IGF-1, which in turn stimulates follicular development, estrogen production, and oocyte maturation. A systematic review and meta-analysis results suggested that GH addition significantly increased clinical pregnancy and live birth rates especially when GH added to gonadotropins in ovarian stimulation of poor ovarian responders (1). The results of Cochrane review of 14 RCTs (1272 women) on GH in IVF in poor responders has shown a slight increase in mean number of oocytes retrieved with the use of GH for poor responders (MD 1.40, 95% CI 1.16 to 1.64; I^2 = 87%; 12 trials, 1153 participants; low-certainty evidence). High heterogeneity in the analysis for mean number of oocytes retrieved and units of GH used suggests quite different effects according to differences including in trial protocols (populations, GH dose and schedule), so these results should be interpreted with caution(1). Meta-analysis done by

Roger J.et al (2019) on the use of GH in poor responders concluded that GH almost universally appears to reduce the duration of ovarian stimulation and collection of a greater number of oocytes than women who received a placebo. But there is no evidence to demonstrate an increased chance of a live birth for a woman who receives GH for this indication(2).

Dehydroepiandrosterone (DHEA) Supplementation: DHEA is an androgen precursor which is used to improve ovarian reserve in poor ovarian reserve patients. The rationale behind DHEA supplementation is that it will increase intraovarian concentration of androgens which improves FSH receptor expression in granulosa cells and IGF-1 production in turn increasing ovarian response to FSH. In a meta-analysis by wang et al, which included both prospective and retrospective studies, showed significant improvements in all parameters including pregnancy rates, apart from the live birth rate (OR 1.35, 95% CI 0.94–1.94), for women prescribed DHEA. More oocytes were collected (weighted mean difference [WMD] 1.09, 95% CI 0.38–1.80), and there were more metaphase II oocytes (WMD 0.78, 95% CI 0.16–1.40), fertilized oocytes (WMD 0.84, 95% CI 0.42–1.26) and top-quality embryos (WMD 0.60, 95% CI 0.34–0.86). Improvements in the clinical pregnancy rate (risk ratio [RR] 1.35, 95% CI 1.13–1.61) and ongoing pregnancy rate (RR 1.82, 95% CI 1.34–2.46) with DHEA supplementation were shown, while the live birth rate (RR 1.35, 95% CI 0.94–1.94) was not significantly different.(3).

Coenzyme Q10: CoQ10 is an essential component of the inner mitochondrial membrane and is responsible for electron transport in the mitochondrial respiratory chain for oxidative phosphorylation leading to the generation of the energy substrate adenosine triphosphate; it also acts as an antioxidant within the oocyte that protects the mitochondria from damage caused by either insulin resistance or oxidative free radicals and improves ovarian response, ovulation and pregnancy in PCOS women (4).

Oral CoQ10 supplementation prior to ovarian stimulation for IVF treatment may improve the ovarian response and the follicular environment, leading to the improved oocyte and embryonic outcomes highlighted by Xu and colleagues(4). however, unfortunately for older patients, they propose that it may be too late to recover from age-related oocyte deterioration, leading to higher aneuploidy rates(5).

Antioxidants: Antioxidants are chemicals that reduce oxidative damage to the tissues. Oxidative stress is the imbalance between the creation of reactive oxygen species and the body's ability to neutralize the effects of reactive oxygen species. Reactive oxygen species and reactive nitrogen species can damage the oocyte, disrupt the final stages of oocyte maturation and impair cumulus cell function, an integral part of oocyte metabolism within the cumulus–oocyte complex(6). A Systematic Review and Meta-Analysis results by Yujie Shang et al showed that use of antioxidants not only significantly increased the number of retrieved oocytes and high-quality embryo rates but also reduced the dose of gonadotropin, contributing to higher clinical pregnancy rates(7).

Metformin: Metformin is usually used as an adjunct therapy to reduce the risk of developing ovarian hyperstimulation syndrome in PCOS women undergoing Gonadotropin-releasing hormone (GnRH) agonist long protocol and antagonist protocols in IVF/ICSI.

Glucocorticosteroids: reduce adrenal androgen production by negative of feedback inhibition of adrenocorticotrophic hormone production. Hence, it benefits women with hyperandrogenic anovulation/ WHO II / Phenotype A and B - PCOS. The mechanism of action presumably involves a reduction in adrenal androgen secretion, which in turn may reduce total circulating androgen levels by as much as 40%, improving folliculogenesis. Glucocorticoids have been proposed as a useful adjuvant to both clomiphene citrate (CC) and gonadotropin ovulation induction, improving ovulatory function, and reducing resistance to ovulation induction agents. Glucocorticoids have positive effects on the ovarian response to stimulation. Some studies (8,9)showed that dexamethasone may influence follicular development and oocyte maturation directly, via 11β-HSD1 in granulosa cells , or indirectly, by increasing serum growth hormone and intrafollicular IGF-1 levels.(8,9). The activity of 11β-HSD in ovarian follicular fluid has even been suggested as a predictive marker for IVF outcomes. Study done by Liu S et all suggested that low-dose oral dexamethasone in women with high progesterone levels in the early proliferative phase sensitized the ovary to gonadotropin stimulation, leading to the secretion of less progesterone, and the dexamethasone group showed a higher cumulative live birth rate than the control group.(10) Typical dosages are dexamethasone 0.25-0.5mg or 5-10mg of predinisolone.

MELATONIN not only regulates the body's seasonal and circadian rhythms; but also delay ovarian senescence, regulate ovarian biological rhythm, promote follicles formation, and improve oocyte quality and fertilization rate. 3mg per day from day 2 to day 6 along with clomiphene may improve, conception and live birth rates.

L-ARGININE supplementation during controlled ovarian hyperstimulation in poor responders decreases blood flow resistance in both perifollicular and uterine arteries. It modulates the permeability of follicular epithelium to plasma proteins and increasing uterine perfusion, might improve ovarian response, endometrial receptivity, and pregnancy rate.

Inositol: Myoinositol is the most commonly found form of inositol. MI has been found to be essential for the proper maturation of oocytes, and its higher concentration in human follicular fluid is considered as a marker of high oocyte quality.(11)

Micronutrients: Micronutrients play a critical role in the success of In Vitro Fertilization (IVF) by supporting various physiological processes essential for fertility and healthy pregnancy.

- Folate (Vitamin B9): Essential for DNA synthesis, repair, and methylation. Folate is crucial for oocyte quality and proper embryo development.

- Vitamin D: Low Levels of Vitamin D, Trace Elements Linked to Premature Ovarian Failure. Vitamin D deficiency is prevalent in PCOS women especially with obesity.
- Vitamin E: Acts as an antioxidant, protecting cells from oxidative stress. It plays a role in reproductive health by maintaining the integrity of cellular membranes.
- Zinc: Zinc is important for oocyte development and may contribute to higher fertilization and pregnancy rates.
- Selenium: It is an antioxidant which protects against oxidative stress and supports thyroid function. Adequate selenium levels may improve embryo quality and implantation rates.
- Omega-3 Fatty Acids: Omega-3 supplementation may improve ovarian function, oocyte quality, and endometrial receptivity, leading to better IVF outcomes.
- Iodine: Iodine deficiency can lead to hypothyroidism, negatively affecting ovulation.

N-acetyl cysteine (NAC): It is a mucolytic agent and has a role in the treatment of infertility. A limited number of studies conducted in the recent years has reported possible benefits of improving insulin sensitivity and better outcomes in ovulation induction in patients with PCOS(12). NAC 1.2gm/day along with Clomiphene from Day 3 for 5days has shown increased ovulation rates.

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SUMMARY

A series of new technologies and adjuvant therapies have been advocated in order to improve the success of IVF treatment. These include add ons in each step of treatment offered to infertile couple. These can vary from improving oocyte, sperm health to add ons for ovarian stimulation and add ons in embryology lab. This review focuses on add ons used in Ovarian Stimulation. It is looking into current evidence to justify the use of these co-interventions and whether some of them can be offered in a personalised patient care.

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