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Editorial

Infertility is a well-known cause of disharmony and disgrace among couples since time immemorial[1,2]. Prior to the 1960s, infertility was almost exclusively a diagnostic statement Infertility treatment started 50 years ago with the use of exogenous gonadotrophins[3]. Controlled ovarian hyper stimulation combined with IUI of capacitated sperm (COH-IUI) has been used to treat to subset of couples infertile in the absence of mechanical compromise of the pelvic viscera, in whom no other efficacious treatment options exist[4,5,6]. For COH in IUI cycles, ovulation induction protocols are Clomiphene citrate Cc. Aromatase inhibitor (Letrozole) alone. or in combination with gonadotrophins (hMG or rFSh), human chorionic gonadotrophins (hCG) used at the end of the stimulation phase to achieve final maturation of the oocytes. The addition of IUI to Letrozole increase fecundity in couples with unexplained infertility or surgically treated endometriosis. [7,8]

Ovarian stimulation with Letrozole is associated with acceptable pregnancy rates compared with gonadotrophins (cumulative pregnancy rate per couple: 24% vs. 36%)[9], with significant less cost, risk and patient inconvenience. One of the earliest observational cohort studies in poor responders in a stimulated intrauterine insemination (IUI) programme used a sequential regime of letrozole for 5 days followed by gonadotrophin injections.[10] There were significantly more mature follicles using significantly lower dosage of gonadotrophin when compared with previous failed IUI cycles, with the clinical pregnancy rate of 21%.

It was followed by the first RCT on the use of letrozole in POR in IVF treatment cycles published in 2004.[15] The study used concurrent treatment with letrozole and recombinant gonadotrophin in a long protocol GnRH agonist regime. The study confirmed the findings from IUI of significantly lower dosage of gonadotrophins with a comparable pregnancy rate. Further trials used simultaneous regimen of letrozole and gonadotrophins in a GnRH antagonist protocol.[16,17,18] One observational study revealed a better implantation rate with a more favourable follicular fluid hormonal profile,[19] and one RCT confirmed the use of lower dosage of gonadotrophins and lower cancellation rate owing to poor response.[20]

Recently improvements in IVF embryology with better fertilization rates and embryo quality mean that fewer oocytes are required by the laboratory. Advances in embryo cryopreservation with the use of vitrification have improved pregnancy rates in frozen embryo transfer cycles, and increasing use of single embryo transfer in good prognosis cases has again reduced the need for many embryos and over the last decade, the concept of 'mild' stimulation has emerged.[11]

These developments have allowed adoption of mild stimulation followed by elective single-embryo transfer, a policy that has been shown in a randomized controlled trial to achieve a similar live-birth rate over 1 year time when compared with conventional IVF with double-embryo transfer.[12] The cost related to the pregnancy complications brought along by the multiple pregnancies resulted from ART treatment could be greatly reduced with the use of mild stimulation protocol with elective single-embryo transfer,[13] and mild stimulation would significantly reduce the possibility of OHSS. Both embryo quality and endometrial receptivity may be improved in the more physiological hormonal environment seen with mild stimulation.[14]

Use of letrozole instead of gonadotrophins would greatly reduce the number of injections needed in a cycle of treatment, reducing the burden placed on the patient and getting the popularity day by day. The short half-life of letrozole would allow it to be completely cleared from the circulation by the time of blastocyst transfer on day 5 following oocyte collection, avoiding risk of teratogenicity.

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