Review

Refining ovarian stimulation in ART

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It is estimated that of all the couples who embark on infertility treatment up to 10% will require some form of Assisted Reproductive Techniques (ART)[1]. ARTs are defined as the techniques used where there is a need for in-vitro preparation or manipulation of gametes. The commonest ARTs are intra-uterine insemination (IUI), invitro-fertilisaion (IVF), and intra-cytoplasmic sperm injection (ICSI). All assisted conception treatments require significant investment in infrastructure, training of personnel and a reliable supply of drugs and other resources. Therefore the high cost of ARTs is a reality the world over. Despite this ART clinics have started to come up in developing countries including Sri Lanka although mostly in the private sector. Parallel to this, efforts are also been made to develop simplified and low-cost assisted conception techniques such as minimal stimulation cycles and intra-vaginal culture although none of these has been evaluated in clinical trials[2].

For ovulatory dysfunction with no other abnormality (normal semen analysis and patent fallopian tubes), ovulation induction is the initial treatment. Clomiphene citrate is the first line of treatment for this purpose due to its simplicity, safety and cost. Clomiphene achieves about 70% ovulation and combining it with timed intercourse will achieve pregnancy of up to 25% per cycle[3]. Letrozole and tamoxiphene can be tried in women who do not respond to treatment with clomiphene. The next step in the treatment is ovulation induction with gonadotrophins, which can be combined with intra uterine insemination[4].

Optimizing pregnancy rates per cycle is the real basis for ovarian stimulation protocols in ART. Although the first successful case of IVF in 1978 was on a natural cycle ovarian hyperstimulation regimes evolved throughout the world in years that followed. These protocols, aiming at generating high counts of oocytes were meant to counter balance inherent shortcomings in in-vitro oocyte fertilization, embryo culture, and embryo transfer. In addition multiple embryos were transferred to maximize pregnancy rates at great expense of multiple pregnancies. These are associated with much patient discomfort, considerable complication rates including significant risk of life threatening ovarian hyperstimulation syndrome. The cost of medications involved makes the procedure so expensive that makes it only a dream to vast majority of infertile couples especially in developing countries.

Mild stimulation protocols make the stimulation less complex, much shorter, less costly, improves patient acceptability and drastically reduces the complications. On the other hand cancellation rates are much higher with these protocols and some women hyperstimulate even to mild stimulation. Therefore there is no ideal protocol to suit every woman. Hence refining ovarian stimulation involves developing individually tailored regimes for each woman. Ovarian response predictors such as female age, anti-Mullerian hormone (AMH) levels, antral follicular count (AFC), presence of poly cystic ovaries (PCOS), and body weight are important in deciding on individualsed regimes.

Controlled ovarian hyperstimulation (COH) in ART

Pre-treatment of patients with oral contraceptive pills, particularly women with poly cystic ovarian syndrome is believed by some to contribute to quality of oocyte with added benefits of better cycle control, better scheduling and adequate suppression of gonadotrophins.

There are two basic protocols for COH in ART. The long GnRH analogues (GnRHa) protocol and the ultra short flare protocol. The long GnRHa protocol is associated with a good oocyte recovery rate, reasonably good fertilization rates, and acceptable pregnancy rates[5]. This protocol has been practiced throughout the ART centres over the past decade and therefore is time tested. The current trend is to shift the emphasis from quantity to quality. This means producing small number of oocytes with better quality. In this protocol GnRHa is started on day 21 of the cycle and continued for 10–14 days till complete down regulation is achieved. Ultrasound criteria of down regulation are small follicles of less than 5 mm and endometrial thickness of 4–5 mm. The E2 level should be less than 50 pg/ml. Once down regulation is confirmed stimulation can be started with FSH or hMG. Ultra sound is done on the 6th day to monitor the stimulation. A good responder is expected to show at least 1–2 follicles of more than 12 mm and 3–4 follicles

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of 8–10 mm with an endometrial thickness of at least 5–6 mm and E2 not less than 300 pg/ml. Once at least 3–4 follicles reach 17–18 mm and endometrial thickness of 8 mm, hCG 5000–10000 i.u. is given followed by ovum pick up 36 hours later.

In recent years the focus of ovarian stimulation has shifted from quantity to quality, meaning that we are concerned more of the quality of the oocyte than its quantity. The objective of this is to produce more of diploid embryos of good quality with optimal implantation potential and not aneuploid embryos which are rejected. The development of GnRH antagonists in recent years has contributed greatly to achieve this objective. There is a global switch to short protocol of GnRH antagonist which has obvious advantages to both the patient and the clinician. The role of LH in healthy folliculogenesis is well understood. Throughout the journey of oocyte, beginning with meiosis 1 stage, LH in the antral follicle plays the constructive role. LH has been shown to exercise different physiological roles at different stages of COH. GnRH antagonists block GnRH receptors by competitive binding resulting in immediate gonadotrophin suppression, which enables short regimen for ovulation induction. Maximal suppression of endogenous LH production occurs very shortly, within 4 hrs of injection[6]. The relative half-life of 13 hrs of GnRH antagonist and rapid and complete recovery of pituitary suppression after discontinuation makes it more appropriate than GnRHa for effective prevention of LH surge. Therefore GnRH antagonists have following advantages over GnRH analogoues when used in controlled ovarian hyperstimulation regeimes.

1. No initial flare-up – The initial flare effect of GnRHa treatment for the first 3 days is associated with a rise in FSH and LH which in many cases leads to cyst formation and need to drain if it does not resolve. Complete pituitary suppression, takes about 14–21 days with GnRHa. In contrast with GnRH antagonist there is immediate suppression of FSH and LH and no cyst formation[7].
2. No estrogen deprivation – In long GnRHa protocols a phase of hypoestrogenimia is induced. Women complain of hot flushes, insomnia headaches etc during this period frequently[8]. In GnRH antagonist protocols this phase does not take place.
3. Shorter treatment cycle – duration of exposure to GnRH antagonist is much shorter.
4. Total doses of gonadotrophins required are less – Higher doses of gonadortophins are required in GnRHa protocols[9].

However, certain studies have shown that the pregnancy rates of GnRH antagonist regimes are marginally lower than what can be achieved with time tested GnRHa protocols[10].

Prevention of ovarian hyper-stimulation syndrome (OHSS) is also of prime concern in refining ovarian stimulation protocols. Every woman with the potential of developing OHSS, undergoing COH, flashes signals/signs to the physician. It is up to us to pick up these signals and act accordingly. Therefore protocols need to be individualized as a preventive measure. In high risk individuals it is safer to start with minimum dosage and follow step up strategy in the event of inadequate response. Coasting is an effective way of preventing OHSS. Coasting is not detrimental to oocyte quality or number. Coasting for 48 hours is a safe measure. More than 48 hours of coasting has been associated with reduced oocyte quality. No medication whatsoever is given during the period of coasting. Coasting is usually done prior to giving hCG. Another effective way is to substitute hCG by GnRHa in the dosage used for down regulation provided the cycle has not been down regulated with GnRHa.

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