Mild and Minimal COH in ART

Sang Hoon Lee

ChungAng University Hospital

The first baby conceived through in vitro fertilization (IVF) will be 20 years old. Since then, IVF techniques have improved in various areas to raise the success rate, to extend the list of pathologies which can be overcome and, therefore, to break down the barriers of infertility.

However, this 'exploration' in the available technologies has increased the burden on the couple and, more recently, on the gametes and embryos themselves.

The ovarian stimulation protocols have increased the amount of drug injected from clomiphene citrate to the association of gonadotrophin and gonadotrophin-releasing hormone agonist (GnRH-a). GnRH-a have almost suppressed the onset of premature lutenizing hormone (LH) surges and, therefore, reduction the cancellation rate. They also allow us to manage the activity of IVF teams more easily. However, the price paid by the patients is not negligible. Ovarian hyperstimulation syndrome (OHSS) is more frequent with the use of GnRHa and the side-effects with the long protocol are frequent and not always well tolerated by the patient.

High-order ovarian stimulation could be injurious to women's health. Recent reports relating ovarian cancer and ovarian stimulation have not yet been formally proven. Cancer is insidious in its one set, and any damage may appear only after several years. Clinically significant hyperstimulation is a now well-recognized risk factor associated with IVF, leading to mobidity and hospitalization in some patients. There is general agreement that multiple pregnancies, including twins, are still too common in assisted human conception and must be avoided. They are the major causes of maternal and fetal morbidity, the increasing need for intensive care after a premature delivery and also for the subsequent social pressure on mother as they raise twins, triplets or higher multiples. Some concern must be expressed about the vast amounts of steroids released from multiple follicles, and of the potential effects of multiple ovulation on the ovarian follicle pool or of later consequences on the onset of the menopause or its normal progression.

Even when pregnant, the couple can still be exposed to complications. Multiple pregnancies expose the children and their families to complications and difficulties which are usually underestimated. Multiple pregnancies should not be considered as an IVF success, even though progress in obstetrics and neonatology has considerably reduced perinatal mortality rates. In comparison with singleton pregnancies, the chances of having a healthy child are reduced in triplet pregnancies as well as, to a lesser extent, in twin pregnancies. It is appalling to attend medical meetings and see the number of teams routinely transferring four or more embryos and being proud of there 50% multiple pregnancy rates including 15% triple. The availability of selective embryo reduction should not mask the terrible paradox of suppressing the develop-

ment of a medically assisted conception.

The first step of friendly IVF is probably the most difficult how to reduce the complexity of the procedure without altering the success rate? However, one should consider the possibility that some women might want to try three times using a very simple procedure which has a 10% success rate, rather than having a single attempt using a procedure which could give a 30% success rate, but which could also have a 30% multiple pregnancy rate, and/or, 4 month of coping with the physical and emotional consequences of failure. This is in addition to the side-effects of the procedure itself (headache, hair loss, weight gain, libido modification, abdominal pain etc.....) and its cost. Comparisons will have to be made on the respective costs of repeated simple treatments with the classical ovarian stimulation protocols.

Simplification of the stimulation protocol can go in various directions. Reducing the amount of the drug used, reducing the amount of control procedures involved in the monitoring of the cycle, improving our knowledge on embryo implantation and our in-vitro handling of gametes and embryos to give the best implantation rate possible.

In an effort to attenuate the stimulation protocols, the development of GnRH antagonists, and their recent availability for safe clinical use in humans, represent an interesting perspective. Olivennes et al have recently presented data on the use of a GnRH antagonist with a single injection protocol which suppresses the inconvenience associated with GnRHa and reduces both the length of the treatment procedure and the amount of human menopausal gonodotropin (HMG) needed. More recently, Frydman investigated the potential of using GnRH antagonists in spontaneous menstrual cycles. The spontaneous cycle is probably the 'gold standard' of friendly IVF. Moreover, higher quality embryos might be obtained with the natural cycle as suggested by Edward et al. What could be more natural than a natural cycle! However, spontaneous cycles have been almost abandoned, due to their poor pregnancy rates and the frequency of cycle cancellations due to premature ovulation. GnRH antagonists could help to prevent LH surges in spontaneous cycles and could, therefore, reduce cancellation rates.

Edward et al have emphasized the use of relatively minor modifications of the natural cycle, or mild forms of priming follicles, as the way to improve the current status of ovarian stimulation for the majority of patients. They are not aware of any adverse physiological effects of the agonists and antagonists, which would be used sparingly. Their effects seem to be readily reversible. These milder forms of ovarian stimulation could self-administer the two or three injections per cycle. Patients might come back willingly for a second attempt at IVF if their first should fail, and undertake several such simplified forms of treatment. More higher-grade embryos may be produced if follicles and oocytes develop in close association with the natural menstrual cycle, and higher implantation rates may be gained.

1. Soft Stimulation Protocol

Clomiphene citrate (CC), alone or in combination with low doses of gonadotrophins, together with the GnRH antagonists could be introduced again in clinical IVF practice aiming to reduce the total dose of gonadotrophins used and to obtain smaller numbers of better quality oocyte.

The protocol of CC/gonadotrophins has been used extensively in IVF/ET with satisfactory pregnancy rates. The major drawback for the CC/gonadotrophin protocol has been the high cancellation rate, mainly related to premature LH surges, and the lower number of oocytes and embryos obtained. The association of GnRH antagonists to this combination has gained new interest since it could prevent LH rise and could represent an interesting treatment option in selected patients with good prognosis by reducing the side effects, the risks, and the cost. Moreover a simpler procedure could be repeated to reach high cumulative success rate. Thus, Craft et al studied the use of cetororelix in combination with CC/gonadotrohpins in "difficult" patients-poor responders and women with polycystic ovary syndrome (PCOS). CC was given daily (100 mg) from day 2 of the cycle for five day, and gonadotropin injections were ether given daily or on alternative days. Cetrorelix was administered daily, 0.25 mg subcutaneously, from the fifth day gonadotropin stimulation. These encouraging preliminary results are also explored in other ongoing studies with Cetrorelix, combing the multiple dose or the single dose protocols with the CC/gonadotropin stimulation.

2. Minimal Stimulation Protocol

Aiming to simplify the procedure, efforts were made to apply IVF in the natural menstrual cycle. Despite the encouraging fertilization and implantation rates that have been reported, the cancellation rate of 10~30% has rendered this approach rather unattractive to most IVF center. The introduction of GnRH antagonists in clinical practice offers an interesting perspective. Hence, the combination of natural menstrual cycle and the administration of GnRH antagonists in the late follicular phase to prevent the LH surge, is a promising alternative which is currently being studied.

Rongieres-Bertrand et al investigated the administration of Cetrorelix in the late follicular phase together with small amounts of supplementary gonadotrophins, in the natural cycle of 33 women undergoing 44 cycles of IVF with good prognosis. A single subcutaneous injection of 1 mg or 0.5 mg Cetrorelix was administered when E_2 plasma levels reached 100 pg/ml to 150 pg/ml and the leading follicle was between 12 mm and 14 mm. Moreover, daily injections of 150 IU of FSH were given from the time of first Cetororelix injection until HCG administration.

It seems, therefore, that the minimal stimulation protocols based on the spontaneous natural cycle cqn be a possible alternative for good prognosis patients, but their efficiency needs to be confirmed in larger studies.

3. Future Development of Minimal Stimulation Protocols

Firstly, it will result in a reduced duration of stimulation and lower amounts of exogenous FSH. Less monitoring will be required and the chances of short-term complications and long-term risks are expected to be reduced. Although les programmarble, timing may be more controllable by the use of estrogen preparations alone or in combination with gestagens in the luteal phase to postpone menses.

Secondly, the strategy of administering low doses of FSH in the late follicular phase will result in fewer

oocytes being available for IVF than in conventional stimulation protocols. It may also be possible to selectively stimulate the growth of large follicles in the late follicular phase by the administration of low doses of LH.

Thirdly, with the use of GnRH antagonists during the late follicular phase, the final stages of oocyte meiotic maturation can also be induced by the administration of recombinant LH, recombinant FSH, native GnRH or GnRH-a instead of HCG. These approaches are currently under investigation and may further reduce the risk of OHSS.

Fourthly, milder forms of ovarian stimulation for IVF are likely to generate fewer embryos. The transfer of large numbers of embryo to increase 'success' rates per IVF cycle or to compensate for poor laboratory performance can no longer be justified. Higher order multiple pregnancies should not be reduce the risks of multiple pregnancies rather than refining techniques for fetal reduction.

Fifthly, milder stimulation protocols may result in fewer or no spare embryos being available for freezing. However, while the transfer of cryopreserved embryos in subsequent cycles represents additional chances for pregnancy without the need for ovarian stimulation and oocyte retrieval, the true added value of cryopreservation programmes remains to be established. The effectiveness of cryopreservation may also depend on the developmental stage of the embryo.

Sixthly, the duration of an IVF cycle will be significantly reduced with minimal stimulation combined with GnRH antagonist. Moreover, this type of stimulation will be much better tolerated by the patient.

4. Conclusion

In the meantime, simplifying the stimulation protocol should be proposed. This could achieved by reducing the amount of stimulatory drugs used in different protocols, e.g. the stepdown scheme or clomiphene citrate protocol, which has recently been making a come-back in IVF, or by minimal monitoring. Another way would be to propose a minimal stimulating protocol to obtain a lower number of embryos with a high implantation rate. Finally, coming back to the spontaneous cycle and improving its success rate, could represent in interesting alternative with a limited burden for the couple and without multiple pregnancy: the most friendly IVF.

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