**Ultrasound Is the Only Monitoring Modality Necessary For Ovulation Induction**

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Ovulation induction is based on the administration of gonadotropins in order to enhance fertility. Daily administration of the drug causes a supra-physiological increase in serum FSH leading to the recruitment of a larger cohort of follicles, further causes their growth and development, and finally, triggering ovulation of usually more than one follicle.

Ovulation induction is based on the administration of gonadotropins in order to enhance fertility. Daily administration of the drug causes a supra-physiological increase in serum FSH leading to the recruitment of a larger cohort of follicles, further causes their growth and development, and finally, triggering ovulation of usually more than one follicle. In IVF programs, the stimulation process is even more aggressive leading to the development of large number different-sized follicles in order to achieve as many as mature oocytes as possible in one stimulated cycle. This kind of treatment has some detrimental consequences on the patients of which the three major ones are: multiple gestation, ovarian hyperstimulation syndrome and torsion of ovary.

The monitoring process is intended to enable the physician to: 1. Choose the most suitable protocol, to obtain best possible outcome, and trying to avoid complications; 2. Adds to the common pool of information, which increases our knowledge and understanding of human reproduction. In the case of ovulation induction it means: 1. Looking at the patient's baseline parameters; 2. Monitoring ovarian response to treatment; and 3. Completion of therapy. These objectives raise the question of how close monitoring should be? And which tools do we need in order to deliver a safe treatment cycle.

When we consider the best monitoring process for the individual, we have to take into account the following points; 1. Increase patient's comfort by simplifying treatment protocols (i.e., reducing time commitments); 2. Evaluating if the does of gonadotropin administered is optimal; 3. Optimizing the time of hCG administration 4. Avoiding the development of OHSS; 5. Reduce the rate of multiple pregnancies; 6. Taking advantage of significant improvements that have been achieved in embryology and laboratory practice; and 7. Addressing economic considerations. The purpose of this short chapter is to provocatively look at the monitoring system, trying to define a way, which will lead us to safe, cost-effective and well-tolerated procedures.

Previously, monitoring of ovarian function was based mainly on measuring serum estradiol concentrations, and results were interpreted in relation to the success rate and development of OHSS. It was previously shown that complications were not dependent on monitoring as such but on the protocol of stimulation (1). Monitoring as a whole cannot prevent the complications but leads us to the point we would like to reach. In ART cycles, the goal is to retrieve mature oocytes and this goal can not reached by measuring estrogen only, since the maturity of the oocyte is closely associated to the size of the follicle, a parameter which can accurately be measured by ultrasound. In addition to the size of the follicles, it has been shown that the best bio-assay for serum estrogen concentration, and also a major factor in the implantation process is the endometrial thickness and its ultrasonographic texture, a parameter which, again, can adequately be measured by ultrasound. Based on the above, the question is whether or not by performing repeated ultrasound scans, safe monitoring can be delivered. To answer this we have to demonstrate that ultrasound can adequately monitor the process of down-regulation, follicular and endometrial development and timely administration of hCG, with no decrease in overall pregnancy rates and no increase in the OHSS rate. Barash et al. (2) looked at the possibility to determine pituitary down-regulation after GnRH-agonist administration (long protocol) by transvaginal ultrasonographic measurement of endometrial thickness. The study was a prospective one investigating 181 patients undergoing 265 IVF-ET treatment cycles. Pituitary down-regulation, defined as a serum E2 concentration <55 pg/mL, was achieved in 77% (204 of 265) of the cycles. An endometrial thickness of <6 mm was found in 92.2% (188 of 204) of cycles in which down-regulation was achieved. An estradiol level of <55 pg/mL was
present in 95.9% (188 of 196) of cycles with endometrial thickness of <6 mm. Therefore, it was concluded that a state of relative hypoestrogenism after GnRH-agonist administration, indicative of pituitary down-regulation, can be predicted with a high degree of accuracy by ultrasonographic measurement of endometrial thickness. Thus, routine testing for serum E2 concentration may be safely omitted.

Furthermore, in another study by the same group (3) the influence of aspiration of functional ovarian cysts on endometrial thickness was investigated. In a prospective study, 22 patients in whom administration of a GnRH-agonist (long protocol) failed to induce pituitary desensitization, as was evident by a serum E2 concentration >55 pg/mL and the presence of an ovarian cyst of >20 mm in diameter, transvaginal ultrasonographic-guided cyst aspiration was performed. Two days later, serum E2 concentration dropped from a mean (+SD) of 203±93 to 37±34 pg/mL. Along with the mean endometrial thickness (9.6±2.0 mm before cyst aspiration and to 5.9±2.4 mm after the procedure). This observation can further support the correlation between serum estrogen concentration and endometrial thickness, allowing to reach a firm conclusion that the down-regulation phase can safely managed by ultrasound only.

Recently, several studies have addressed the question of whether it would be possible to monitor the ovulation induction phase in ART cycles using ultrasound as the only monitoring tool, abandoning serum estrogen measurements. The advantage of using ultrasound only is that this tool can potentially provide simultaneous information on follicular growth and at the same time also on estradiol production by direct measurements of endometrial thickness. In a recent publication by Wikland and Hillensjo (4) these authors described a system in which the majority of ART cycles were monitored by ultrasound alone. In women not at risk for OHSS or poor responders, only one ultrasound scan was performed on stimulation day 9 or 10. It was even found that by comparing the time period in which ultrasound and estrogen measurements were used to the period in which ultrasound alone was used, the take home baby rate was higher and the OHSS rate was only 1.8%.

In a retrospective study, Ben-Shlomo et al. (5) compared the results of 1985 controlled ovarian hyperstimulation cycles during two consecutive periods in between 1996 to 1999. During the first 2 years, an intensive monitoring protocol was used that included both ultrasound and serum E2 levels. In the next 2 years a less intensive protocol was adopted, that did not include serum E2 measurements. Their results showed no difference in the duration of stimulation or the amount of gonadotropins used, number of oocytes retrieved (12.1±9.3 vs. 9.6±6.3), fertilization rates (74% vs. 75%), and clinical pregnancy rates (26.2% vs. 27.9%). The incidence of severe ovarian hyperstimulation syndrome was not significantly different between the two study periods.

The last issue in the monitoring process is whether we can administer hCG in a safe manner that will not put the patient at a higher risk for OHSS without measuring estrogen concentration. In order to answer this question we first have to ask ourselves whether there is an upper-limit to serum estrogen concentration above which we would withhold hCG administration and cancel the cycle. In an extensive search of the literature it was found that only the minority of the physicians would cancel cycle due to high level of estrogen ( >25,000 pmol/l) (6). In such a theoretical case, 11% of the physicians would cancel the cycle, and 66% would take some preventive measures. Among the selected preventive measures, coasting was by far the most popular choice (60%), followed by the use of i.v. albumin or hydroxyethyl starch solution (36%) and cryopreservation of all embryos (33%). Basically, these safety measures are being taken following the ultrasonographic observation of high density multifollicular ovaries, in patients with PCOD, or if more than 30 eggs are being retrieved. In such extreme cases, where coasting would probably be the preferable method for prevention of OHSS, there exists a clear justification to add serum estrogen measurements to the monitoring process.

The other pretending issue is to optimize the time of hCG administration. Is this depend on serum estradiol concentrations? Is it important to schedule the time of administration in a very precise way in relation to estrogen secretion? In an elegant study Tan and his colleagues (7) tried to address this issue. This group of physicians designed a prospective randomized study to look at the optimum time for the administration of hCG after pituitary desensitization with GnRH-agonist. Two hundred forty-seven patients undergoing an IVF treatment cycle with the administration of GnRH-agonist from day 1 of the menstrual cycle were recruited for the study. After pituitary desensitization had been achieved at least 14 days later, ovarian stimulation with hMG was commenced. Ovarian stimulation, cycle monitoring, oocyte recovery, and IVF-ET techniques were identical in all patients. The patients were randomly divided into three groups; group 1 (n = 79) had hCG administered when the mean diameter of the largest follicle had reached 18 mm, at least two other follicles were greater than 14 mm, and serum E2 levels were consistent with the number of follicles observed on ultrasound.
Patients in groups 2 (n = 84) and 3 (n = 84) had hCG administered 1 day and 2 days, respectively, after the above criteria had been reached. Although it was found that the mean day of hCG administration (P < 0.01), maximum serum E2 concentration (P = 0.06), number of days of serum E2 rise (P = 0.03), and mean diameter of the largest follicle (P < 0.001) were significantly different, no significant differences in the mean number of preovulatory and medium size follicles, number of oocytes recovered or embryos transferred was found. There were also no significant differences in the oocyte recovery, fertilization and cleavage rates, in the number of embryos frozen, or in the pregnancy rates per initiated cycle and per ET. Therefore, it was concluded that there is no significant advantage in the precise timing of hCG administration after pituitary desensitization with GnRH-agonist.

Trying to address the monitoring issue in cycles in which GnRH antagonists are being used is somehow more difficult as our experience the optimal monitoring system in such cycles is rather limited. Most of the studies done by now adopted an aggressive monitoring system which included ultrasound along with serum concentrations of estradiol and LH (8). However, these were preliminary studies which were conducted during the “learning curve” of these recently introduced preparation. It can be expected that once our understanding of the dynamics and characteristics of antagonists cycles will be improved, more flexible and practical monitoring schemes will be introduced.

Ovulation induction differs considerably from ART cycles in terms of the aggressiveness of the stimulation protocols and their final goals. Shoham et al. (9) have raised the question of whether it is possible to run a successful ovulation induction program based solely on ultrasound monitoring? In this prospective study, monitoring of ovulation induction was performed using serial ultrasound measurements, in comparison with E2 concentrations that became available at the end of each cycle. Twenty hypogonadotropic and 29 ultrasonically diagnosed polycystic ovary patients received treatment with gonadotropins. The results of this study showed that follicular growth, uterine measurements, and endometrial thickness correlated strongly with E2 concentrations (P< 0.0001). Endometrial thickness on the day of hCG administration was significantly thicker (P< 0.01) in conception (n = 27) compared with nonconception cycles (n = 87), whereas no significant differences were observed in serum E2 concentrations. No pregnancy was observed when hCG had been administered when endometrial thickness ≤ 7 mm. Midluteal endometrial thickness of ≥ 11 mm was found to be a good prognostic factor for detecting early pregnancy (P< 0.008). It was therefore concluded that serial ultrasound examinations used alone have proven to be safe and highly efficient. Ultrasound also had the unique ability to predict pregnancy in the midluteal phase. However, since in gonadotropin stimulation without GnRH analogues premature LH rise or luteinization may occur, some clinicians would advocate a monitoring system which includes either serum LH or progesterone along with estradiol in order to accurately time hCG administration.

**Conclusion**

With the introduction of GnRH agonists for pituitary down-regulation combined with gonadotropins for ovarian stimulation in became clear that hormonal monitoring of the follicular maturation is not so crucial. Monitoring of stimulation can be done only by means of ultrasound, and in case of high suspicion for the development of OHSS, additional measures can be taken either before or after aspiration. Such a monitoring system will simplify the treatment and its cost. The situation is the same in patients who are undergoing conventional ovarian stimulation. In these patients, since we are bound to prevent multiple gestation, the final stage of ovulation will not be triggered if there will be more than 2 to 3 leading follicles. By keeping this limit, it is quite rare either to reach high levels of serum estradiol or to develop OHSS and thus measuring serum estrogen levels will not add significantly to efficacy or safety of the treatment. The above simplification of the monitoring protocols will increase both cost-effectiveness and patients’ convenience.

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