CHAPTER 13

Clinical problems associated with ovarian stimulation for conventional IVF (excluding OHSS)

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INTRODUCTION

Although the world's first IVF baby Louise Brown was conceived within a natural menstrual cycle[1], it soon became obvious that if IVF was to progress from a research tool to a clinical treatment, the use of controlled ovarian hyperstimulation was necessary. Initially it was the use of clomiphene citrate[2] that was utilized to produce multiple follicles, soon to be followed by injections of gonadotropins[3]. Soon the use of the natural cycle was virtually abandoned and various regimens utilizing follicle-stimulating hormone (FSH) were introduced.

The next breakthrough was the utilization of gonadotropin releasing hormone agonists (GnRH-A)[4], which suppressed luteinizing hormone (LH) release, preventing spontaneous ovulation and allowing hormonal monitoring to be significantly decreased, thus making treatment much easier. More recently, GnRH antagonists have been utilized[5] and allow the suppression of LH with a shorter administration, which is preferred by many patients[6].

There have been many modifications of controlled ovarian hyperstimulation (COH) for IVF but the basic principles remain – the utilization of FSH to recruit more of the developing primary oocytes to progress to maturation rather than atresia, thus giving the clinician more follicles to aspirate, resulting in several oocytes to be inseminated, hopefully resulting in a choice of embryos for transfer, and some for freezing. These protocols of COH are responsible for IVF reaching a success rate which has enabled it to be a readily available clinical treatment for subfertility, the world over.

However, as with most things in life, new procedures and treatments will also have associated with them new problems. The most serious complication of COH is ovarian hyperstimulation syndrome (OHSS), which is a potentially life-threatening complication. This complication is discussed in detail in Chapter 14. In this chapter we will confine ourselves to the discussion of other clinical problems associated with COH for IVF.

CHOOSING THE CORRECT DOSE OF FSH (UNDERDOSING/OVERDOSING)

Choosing the correct starting dose for a COH cycle is important. Administering too low a dose of FSH will result in insufficient follicles maturing, and the cycle may then have to be abandoned with the wasted time, effort, and hormones. Various starting doses for COH

have been developed. Overdosing may result in OHSS, a potentially serious complication. Table 13.1 lists starting dose according to patient's age, basal FSH level, and PCO status, as devised at Monash IVF.

Administering the medication

With the daily use of injectable forms of FSH, administered by healthy patients who are not in hospital, it soon became generalized practice that women should be taught to self-administer. When this responsibility is transferred from the medical/nursing staff, potential new problems of administration arise. Protocols to teach patients and their partners about preparing the medication and administering injections had to be developed, and the techniques had to be taught to the users. Any deviations from dosage or method of administration could have an adverse outcome.

Medication preparation

During the use of the urinary product human menopausal gonadotropin (HMG), the FSH had to be reconstituted from a powder form. Inadequate technique of dissolving the powder or incompletely aspirating the contents of the ampule would result in underdosing. With the recombinant product, rFSH [Gonal-F (Serono, Geneva) and Puregon® (Organon, Oss, The Netherlands)], the hormone comes as a solution ready to use, thus avoiding preparation errors. With the recently developed pens, administration has become even easier, and mistakes in dosing should be far fewer.

The triggering of follicular maturation is still mostly by human chorionic gonadotropin (hCG), which is supplied in a powder form, and the possible consequences described above still apply. However, recombinant LH is now available as Luveris (Serono, Geneva), which comes in a solution form thus avoiding the problems of preparation.

Hormone storage

With gonadotropins being supplied in a solution rather than powder form, in order to maintain efficacy, stricter conditions with regard to temperature for storage apply. Both Puregon and Gonal F need to be stored in a refrigerator, between 2 and 8°C.

Table 13.1 Starting dose of follicle-stimulating hormone for IVF as used at Monash IVF

RECOMMENDED DAILY DOSE OF FSH				
Patient criteria			*FSH dose*	
Female age	*day 3 FSH*	*PCO/ PCOS*	*Recombinant FSH Puregon®*	*Recombinant FSH Gonal-F® with metformin*
<38	≤10	No	200	225
<38	>10	No	450	450
<38	≤10	Yes	150	150
≥38	≤10	No	200	225
≥38	>10	No	450	450
≥38	≤10	Yes	200	225

For subsequent cycles, the dose may be adjusted when previous response to FSH is reviewed

Injecting technique

When gonadotropins were first utilized it was standard practice to administer them by intramuscular injection, However, it was shown that subcutaneous administration of FSH was just as effective. Of course subcutaneous injections were much easier and could be self-administered. FSH pens are even more user friendly.

ADMINISTERING THE RIGHT MEDICATION – NEED FOR hCG

One of the commonest reasons for failing to recover oocytes from preovulatory follicles is the failure to administer hCG at the appropriate time prior to oocyte collection. Usually hCG is administered 34 to 38 h prior to planned oocyte collection.

What to do if there is doubt about hCG administration?

If several preovulatory follicles have been drained and no oocyte has been recovered, it is recommended that follicular fluid be tested on an hCG dipstick to ensure the presence of hCG within the follicles[7], confirming that the appropriate dose of hCG has been administered. If the test is negative, re-administration of hCG and postponing the oocyte collection until 36 hours after the administration of hCG should be considered.

LUTEAL SUPPORT

It is generally accepted that in cycles where the GnRH agonist has been used there is a need for luteal support. Because of the increased risk of OHSS with booster doses of hCG, it is now routine practice to administer progesterone (P_4) supplementation during the luteal phase in the form of progestogen, either as progesterone pessaries, vaginal cream progesterone 8%, 90 mg/1.125 g gel, prolonged release (Crinonone, Serono, Geneva), or by injection.

Side-effects of P_4 administration

Some women complain of both local and generalized side-effects from the use of vaginal progesterone, as characterized by premenstrual symptoms. Both vaginal preparations can cause local vaginal irritation.

MONITORING

Ultrasound

The main method of monitoring the ovarian response to COH is to follow the growth and development of ovarian follicles. Ultrasound gives a physical measurement of the number and size of follicles that are developing. It is therefore imperative to have a reliable transvaginal ultrasound monitoring service available, in order to make decisions about the timing of hCG administration and subsequent oocyte recovery. Any limitations of such a monitoring service will impact on the efficacy of the whole IVF treatment cycle.

Hormonal

With the reliance on ultrasound, the assessment of hormone levels has become less important, although some units still depend on estradiol (E_2) levels to help with decision making. With the use of GnRH agonists and antagonists, the measurement of LH is no longer relevant.

OOCYTE COLLECTION

Anesthesia/analgesia

The analgesia/anesthesia used varies from unit to unit. If general anesthesia is used there are risks

of anesthetic complications, the most common being the risk of vomiting and inhaling. With intravenous sedation, the cough reflex is maintained and the risk of inhalation is far less likely. There have been no anesthetic complications at Monash IVF Clayton in 18 000 oocyte collections during the last 15 years.

Surgical trauma

When the technique of transvaginal oocyte collection under ultrasound control was first utilized, there was concern about possible complications of blind transvaginal puncture of the ovary. Fortunately time has shown that complications are very rare. With the hyperstimulated ovary resting next to the upper vagina, the aspiration needle can enter the ovary without damage to the bowel or other organs. Sometimes the ovary is behind the uterus, and oocyte collection is only possible by passing the needle through the myometrium. This does not seem to lead to complications in most instances.

The stimulated ovary lies adjacent to the iliac vessel, and on transverse ultrasonic view they may appear like follicles, but damage to the vessels is also rare. Initially, to reduce the risk of introducing the needle too deeply, an injection gun was developed. The operator measured the distance of the follicle from the end of the needle guide, and this distance was preset. The needle was spring loaded, and a trigger was released which then fired the needle into the follicle. As operators became more comfortable with ultrasound guided follicle puncture, freehand needling has become universally used.

Bruising/discomfort

It is fair to say that most women experience some degree of postoperative discomfort. This can be due to 'bruising' of the ovary due to the multiple punctures, to distension of the follicles with blood postoperatively, or the oozing of blood from the drained follicles causing some degree of peritoneal irritation. The degree of discomfort is usually moderate, and whilst some women require some parenteral analgesia (usually a narcotic) immediately postoperatively, subsequently women can manage with oral analgesics. If severe pain persists, or especially if it develops some time after the oocyte collection, a complication should be suspected.

Bleeding

When oocyte collections were performed laparoscopically, it became apparent that the aspirated follicle filled with blood, and there was subsequent intraperitoneal bleeding. This bleeding was self-limiting, and the need for any surgical intervention was very rare. It was hoped that transvaginal oocyte collection was going to be just as safe, although the inability to inspect the pelvis postoperatively did cause some concern. With 20 years of experience behind us, we are now confident that postoperative bleeding is rare, and is usually self-limiting.

Bleeding can occur either from the ovary intraperitoneally, or from the vaginal skin, vaginally. It is our practice, that, if vaginal bleeding is excessive at the end of the procedure, an intravaginal pack is inserted to apply local pressure for about one hour. The pack is then removed and bleeding is almost always controlled. I personally have never used suturing of the vaginal vault to control bleeding, although this is occasionally performed at Monash IVF. With intraperitoneal bleeding a pelvic hematoma may result, which is then the basis for pelvic infection. This is discussed below under 'infection'.

Organ damage

With transvaginal scanning an excellent view of the ovaries is obtained, and with manipulation of the probe, the vaginal vault can be brought adjacent to the ovary. Bowel shadows can be

identified and differentiated from the ovary. With some experience, freehand puncture can be safely carried out with little risk to other organs. There is some danger of perforating the ovary and damaging organs behind, and this was the reason for developing the 'aspiration gun'. However, it soon became apparent that freehand control was good, and rarely resulted in organ damage.

Infection

Because of the sensitivity of oocytes to antiseptics, the vagina is not sterilized prior to oocyte collection. Consequently, a sterile needle is inserted through the vagina, potentially pushing organisms from the vaginal flora intraperitoneally. Initially it was thought advisable to cleanse the vagina with saline or sterile water, but subsequent advice was that this just activated the vaginal organisms. Most clinicians use no preparation of the vagina, and fortunately we have learnt with time that the infection rate is low, although it does occur in 1 in 300 oocyte collections. Although usually not serious, and responsive to a course of antibiotics, the infection can sometimes be more severe and pelvic abscess may result, requiring drainage.

Ovarian torsion

This is a very rare complication of oocyte collection from a hyperstimulated ovary, where torsion resulting in gangrenous necrosis of the ovary may result. Suspicion of ovarian torsion should be aroused if the woman experiences a disproportionate amount of vomiting associated with localized pain. Clinical signs are that of an acute abdomen, and laparotomy is urgently required. If the blood supply appears intact after untwisting, conservative surgery can be undertaken, but if there is irreversible avascular necrosis, then oophorectomy needs to be carried out.

CONCLUSIONS

In a publication on in-vitro maturation (IVM) of oocytes, it is necessary to conclude with a comparison of what advantages this new technique has to offer over conventional COH. Of course in the absence of the use of significant doses of FSH, OHSS will not occur. Underdosing also is not relevant as it is the ovaries 'decision' how many primordial follicles it has available. As less medication has to be administered, the possibility of administering the wrong medication is decreased. Monitoring is less frequent than for stimulated cycles.

The clinical problems after oocyte collection are also somewhat different. The method of anesthesia is probably no different for IVM compared to COH, so the risks would be no different. Whilst the stimulated ovary after COH is bigger and maybe more vascular, the risk of the relative difficulty of aspirating small follicles probably balances the risk of trauma. Bruising and discomfort is less with IVM, as the ovaries are less vascular and do not fill up with blood, thus avoiding the discomfort caused by distended cysts. Bleeding is less common, as the unstimulated ovary is far less vascular. With respect to the risk of infection, there are no data yet available to compare postoocyte collection infection rates, but from first principles, as the blood filled ovarian follicles act as excellent culture media, their absence after IVM should result in a lower infection rate. As ovarian torsion is principally caused by distended blood cysts making the ovary uneven in consistency, this should not occur after unstimulated IVM.

In summary, as the lack of stimulation results in less disruption of the ovary, the consequences and complications of oocyte collection should be less severe and less common than after oocyte collection for IVF. We will have to wait until larger series of IVM are reported before we can confirm these advantages. The most significant advantage of IVM with respect to complications is the absence of OHSS, which is the most com-

mon significant, occasionally life threatening complication of COH.

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