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Guidelines for use of gonadotrophins

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1 INTRODUCTION

This guideline addresses the clinical use of gonadotrophins in induction of ovulation and ovarian stimulation with or without assisted reproduction technology.

2 USE OF GONADOTROPHINS

2.1 Ovulation induction

Gonadotrophin therapy is indicated in patients with hypogonadotrophic hypogonadism and with normogonadotrophic anovulation who failed to ovulate on clomiphene citrate (CC). Other infertility factors should be assessed before embarking on this therapy, which is associated with risks. The male partner should have semen analysis performed while the female partner should have a test of tubal patency.

Gonadotrophin treatment is very effective in inducing ovulation and the results depend on the indication and the regimen employed[1]. The 6-month cumulative pregnancy rate in patients without polycystic ovary syndrome (PCOS) is around 90% with an abortion rate of 25% whereas the corresponding rate in PCOS is only 50-60% with an abortion rate of 30-40%.

2.2 Ovarian stimulation

Many infertile women with normal ovulatory cycles are now receiving gonadotrophin therapy to induce development of multiple ovarian follicles in an effort to try to improve the chances of conception in any given cycle. This can be used in conjunction with natural intercourse or artificial insemination[2-4].

Ovarian stimulation is being used in the majority of assisted reproduction methods in order to improve the success rate by increasing the number of oocytes and thus the number of embryos to be replaced.

3 CONCERNS WITH GONADOTROPHIN

3.1 Multiple pregnancy

Both ovulation induction and ovarian stimulation may result in unpredictable numbers of follicles and hence oocytes. Patients with polycystic ovaries may be particularly at risk. Multiple pregnancy occurs in approximately 15-20% of cases following gonadotrophin induced ovulations. Measures should be taken to avoid these multiple pregnancies whenever possible because of the increased likelihood of pre-term deliveries and the higher perinatal morbidity and mortality associated with delivery of small pre-term infants[5].

During ovulation induction, a lower starting dose of gonadotrophin is preferred and careful monitoring by ultrasound examination provides good assessment of ovarian response in terms of the number of developing follicles. It has been recommend that cycles with more than two follicles >16 mm in size should be cancelled in order to reduce the risk of multiple pregnancies and the

starting dose of the drug should be reduced in the next cycle[6]. The number of intermediate-sized follicles will also have to be taken into consideration. When hCG is withheld because of the risk of OHSS and/or multiple pregnancy, the couple should be warned of such risk and to avoid sexual intercourse or to use contraception. Other options such as converting ovulation induction cycles to IVF treatment with replacement of two embryos only and aspirating supernumerary follicles can also help to reduce the risk of multiple pregnancies. When multiple pregnancies occur in spite of these measures, selective fetal reduction may be considered. However, selective fetal reduction is not without complications and it should never be considered a substitute for careful monitoring.

The risk of multiple pregnancy during IVF treatment depends on the number of embryos replaced[7-8].

3.2 Ovarian hyperstimulation syndrome (OHSS)

OHSS is a serious and potentially life-threatening complication of ovulation induction and ovarian stimulation, usually arising from excessive ovarian stimulation. Before offering gonadotrophin therapy, every patient should be properly counselled about the risk of OHSS associated with the method used and educated on the presenting symptoms. Patients at risk of the syndrome are identified and different measures can be taken to prevent the syndrome or reduce the risk. Ovulation induction cycles with excessive response can also be converted to IVF treatment, in which the aspiration of follicles may have a protective effect against OHSS. Administration of intravenous albumin at the time of oocyte retrieval may be of benefit in prevention of severe OHSS in high-risk cases[9]. Clear guidelines on the management should be available[10].

3.3 Ovarian cancer

Recently, there has been increasing concern about a possible link between drugs given for ovulation induction or ovarian stimulation and development of ovarian cancer[11-12]. Infertility is an independent risk factor of ovarian cancer, separate from any effects of nulliparity, which in itself doubles the risk of ovarian cancer. Patients receiving gonadotrophin therapy should be informed that we are aware of this particular concern but the available evidence does not lead to the conclusion of a firm link between fertility drugs and ovarian cancer[13]. It also seems prudent that gonadotrophins are given at the lowest effective doses and limited to the least number of cycles.

4 GONADOTROPHIN PREPARATIONS

Hypogonadotropic hypogonadal women who have very low serum LH concentrations should be given a gonadotrophin preparation containing both FSH and LH because of the fundamental role of LH in ovarian steroidogenesis. When recombinant FSH is offered to these women, follicular development is satisfactory but serum oestradiol concentration remains low and the endometrial lining is thin.

Both urinary gonadotrophin and recombinant FSH are equally effective for inducing ovulation in women with CC-resistant PCOS [14].

A meta-analysis[15] of randomized trials on IVF cycles demonstrated that the use of urinary or recombinant FSH was associated with a significantly higher clinical pregnancy rate than human menopausal gonadotrophin. A more recent meta-analysis[16] by the same group further indicated that recombinant FSH was superior to urinary FSH in terms of the pregnancy rate. However, it is still controversial whether recombinant FSH results in a higher pregnancy rate than urinary gonadotrophins when use of different regimens of pituitary desensitization are also taken into consideration[17].

In addition to the effectiveness, there are differences in safety (including the theoretical risk of transmitting Creutzfeldt-Jakob disease through contaminated urine extracts and allergic reaction) and cost between urinary and recombinant preparations[18].

5 ADJUVANT THERAPY

5.1 Gondotrophin-releasing hormone (GnRH) agonists

The use of GnRH agonist prior to gonadotrophin administration will lower the tonic high LH levels in the follicular phase of PCOS patients and prevent the occurrence of premature LH surges or premature luteinisation. This may reduce the associated high abortion rate. A recent meta-analysis[19] of three randomised trials shows that there is no clear advantage in the routine use of GnRH agonist in conjunction with gonadotrohphin for ovulation induction in patients with CC-resistant PCOS. Moreover, the use of GnRH agonist will further increase the cost of gonadotrophin treatment because of the GnRH agonist and the increased amount of gonadotrophins used after using GnRH agonist. Therefore, routine administration of GnRH agonist with gonadotrophin is not indicated in ovulation induction. It may be more appropriate to use GnRH agonist in women who show evidence of premature luteininisation in previous gonadotrophin treatment cycles.

On the other hand, the routine use of GnRH agonist in assisted reproduction cycles significantly reduced cancellation rates, increased the number of oocytes recovered, and improved pregnancy rates[20].

5.2 Gonadotrophin-releasing hormone (GnRH) antagonist

GnRH antagonists immediately suppress the secretion of gonadotrophins from the pituitary gland after administration. Many clinical studies have confirmed the efficacy of the GnRH antagonists in the prevention of premature LH surges during ovarian stimulation in assisted reproduction cycles and their safety, whether they were given as multiple daily doses or as a single dose. Compared with the use of GnRH agonist in the long protocol, GnRH antagonist is associated with shorter duration and lower dosage of gonadotrophin but a significantly lower pregnancy rate (Odd ratio 0.79; 95% confidence interval 0.63–0.99)[21].

5.3 Insulin sensitising agents

Insulin resistance and compensatory hyperinsulinemia play significant role in the causation of anovulation in women with PCOS. Therefore, insulin sensitizing agents such as metformin have been widely used for ovulation induction when there is no response to CC in patients with PCOS[22]. Some studies[23,24] could not demonstrate improved ovulation rate after taking metformin, with or without CC.

Treatment with metformin during gonadotrophin therapy for ovulation induction alone or IVF treatment may allow a reduced rate of hyperstimulation and reduce the risk of multiple pregnancy[22].

6 RECOMMENDATIONS

6.1 Selection of patients

Treatment with gonadotrophins should be restricted to appropriately investigated couples with a diagnosis in whom such treatment has been shown to be beneficial in view of its costs and risks. Results in relation to patients' age and diagnosis should be considered.

6.2 Welfare of the child

In accordance with Code of Practice on Reproductive Technology and Embryo Research[25], the welfare of any resulting child from the treatment and of other existing children must be considered when offering all types of assisted conception.

6.3 Counselling

Prior to treatment couples must be made aware of the problem of multiple pregnancy and the potential risks this

carries during the antenatal, intrapartum and neonatal period as well as subsequently. The risk of OHSS and its symptoms during development need to be highlighted. The putative risk of developing ovarian cancer after gonadotrophin therapy should be informed.

6.4 Treatment centre

Stimulation of ovarian function with gonadotrophins should be restricted to specialist practice with access to intensive monitoring by plasma or serum estradiol and pelvic ultrasound[6]. Careful monitoring is especially important to allow adjustment of dosage and to avoid OHSS. Such specialist practice centres should also have trained gynaecologists with specialist knowledge and facilities to monitor and treat patients with OHSS should it develop.

6.5 Gonadotrophin preparation

As it is still controversial whether recombinant FSH results in a higher pregnancy rate than urinary gonadotrophins, additional factors should be considered when choosing a gonadotrophin preparation, including the safety, cost, patient acceptability and drug availability.

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This guideline was produced by The Hong Kong College of Obstetricians and Gynaecologists as an educational aid and reference for obstetricians and gynaecologists practising in Hong Kong. The guideline does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognised clinical methods and techniques for consideration by practitioners for incorporation into their practice. It is acknowledged that clinical management may vary and must always be responsive to the need of individual patients, resources, and limitations unique to the institution or type of practice. Particular attention is drawn to areas of clinical uncertainty where further research may be indicated.

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