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Guidelines for use of gonadotrophins

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1 INTRODUCTION

Recent changes in infertility practice have meant that gonadotrophic hormones are now used in a far wider group of infertile patients than merely those with anovulation.

The use of gonadotrophic hormone preparations to induce multiple follicular growth for in vitro fertilization (IVF) falls within the remit of the Provisional Council on Reproductive Technology and the future Council on Reproductive Technology, who will issue their own Code of Practice in relation to treatments covered by the Human Reproductive Technology Bill (1997) recently tabled at the Legislative Council, so are not discussed here.

2 CURRENT USE OF GONADOTROPHINS

2.1 Anovulation

There is good evidence that medical treatments are highly effective in anovulatory infertility where a specific problem in the hypothalamic pituitary axis has been identified. For hyperprolactinaemia, bromocryptine or another dopamine agonist are appropriate first time treatments. Pulsatile administration of GnRH has proven efficacy in selected patients with hypogonadotrophic amenorrhoea and in the remainder of clomiphene resistant patients the use of gonadotrophins is indicated with reported excellent results.

2.2 Polycystic Ovary Syndrome

Treatment of ovulatory dysfunction caused by the more complex hormonal dysfunctions in patients with polycystic ovary syndrome are less effective but the use of gonadotrophins is commonly tried with successful conception. The polycystic ovary may be more sensitive to such treatment regimens and requires particular vigilance or use of GnRH analogue and gonadotrophin regimens.

2.3 Superovulation with Intrauterine Insemination (IUI) or Donor Insemination (DI)

Many “unexplained” infertile women with normal ovulatory cycles are now receiving gonadotrophin therapy to induce multiple ovarian follicles in an effort to try to improve the chances of conception in any given cycle. Used in conjunction with IUI this may be an effective therapy, although only for the first few cycles. IUI without ovarian stimulation does not appear to be an effective treatment when compared to an untreated control group. Many clinics are now using gonadotrophic treatment in donor insemination cycles using the same logic of hopefully improving per cycle fecundity rates from the induction of multiple ovulations.

3 CONCERNS WITH GONADOTROPHIN THERAPY

Induction of ovulation in anovulatory women, or hyperstimulation of ovulatory women, results 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.

The aim should also be to avoid selective fetal reduction being contemplated because infertility treatment has caused a higher order multiple pregnancy.

Ovarian hyperstimulation syndrome with its resultant discomfort and pain, fluid-balance alterations and risk of thrombosis can be a fatal condition and is to be avoided wherever possible. Whilst appropriate selection of patients, treatment protocols, effective and strict monitoring during treatment and withholding human chorionic gonadotrophin (hCG) injections can reduce its rate, the risk cannot be entirely removed in any cycle in which gonadotrophins are administered.

There is no convincing evidence at the present moment that gonadotrophic hormone preparations can cause ovarian cancer. Patients undergoing ovulation induction may be advised that we are aware of this particular concern but the current available evidence is insufficient to implicate or otherwise gonadotrophins.

4 RECOMMENDATIONS

4.1. 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.

4.2. Welfare of the child

As with all types of "assisted conception", the welfare of any resulting child from the treatment and of other existing children, must be considered.

4.3 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 ovarian hyperstimulation syndrome and its symptoms during development need highlighting.

4.4 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. Careful monitoring is especially important to allow adjustment of dosage and to avoid hyperstimulation. Such specialist practice centres should also have trained gynaecologists with specialist knowledge and facilities to monitor and treat patients with hyperstimulation should it develop.

4.5 Multiple pregnancy

In the management of induction of ovulation it is extremely important to prevent multiple pregnancy. In general regimens which minimize or avoid the risk of multiple pregnancy, even at the expense of lower pregnancy rates are recommended. No further gonadotrophins should be given and the ovulatory dose of

hCG should be withheld if there are more than three follicles with maximum diameter of 16 - 18 mm. When hCG is withheld because of the risk of ovarian hyperstimulation and/or multiple pregnancy, the couple should be warned of such risk and to avoid sexual intercourse. The number and size of the secondary cohort of follicles need also to be considered in the timing or advisability to administer further gonadotrophins or hCG (this does not apply to IVF or GIFT cycles).

REFERENCES:

1. Braat DD, Schoemaker R, Schoemaker J. Life table analysis of fecundity in intravenously gonadotrophin-releasing hormone-treated patients with normogonadotropic and hypogonadotropic amenorrhea. Fertil Steril 1991;55:266.

2. Filicori M, Flamigni C, Meriggiola MC et al. Ovulation induction with pulsatile gonadotropin-releasing hormone : technical modalities and clinical perspectives. Fertil Steril 1991;56:1-13.

3. Hull, MGR, Savage PE, Jacobs HS. Investigation and treatment of amenorrhoea resulting in normal fertility. BMJ 1979; 1:1257-61.

4. McFaul PB, Traub Al, Thompson W. Treatment of clomiphene citrate-resistant polycystic ovarian syndrome with pure follicle-stimulating hormone or human menopausal gonadotrophin. Fertil Steril 1990;53:792.

5. Larsen T, Larsen JF, Schioler V et al. Comparison of urinary human follicle-stimulating hormone and human menopausal gonadotropin for ovarian stimulation in polycystic ovarian syndrome. Fertil Steril 1990;53:426.

6. Fleming R, Haxton MJ, Hamilton MPR et al. Combined gonadotropin releasing hormone analog and exogenous gonadotropins for ovulation induction in infertile women : efficacy related to ovarian function assessment. Am J Obstet Gynecol 1988;159:376-81.

7. Martinez AR, Vermeiden JPW, Bernardus R. Pregnancy rate after timed intercourse or intrauterine insemination after human menopausal gonadotropin stimulation of normal ovulatory cycles : a controlled study. Fertil Steril 1991;55:258.

8. Kirby CA, Warnes GM, Flaherty SP. A prospective trial of intrauterine insemination of motile spermatozoa versus timed intercourse; Fertil Steril 1991;56:102-7.

9. Whittemore AS, et al. The Collaborative Ovarian Cancer Group. (1992) Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. Am. J. Epidemiol., 136,1175-1220.

10. Cohen J., et al IFFS Expert Group Report on the Whittemore study related to the risk of ovarian cancer associated with the use of infertilty agents. Hum Reprod 1993;8:996-9

11. Spirtas R, et al Fertility drugs and ovarian cancer: red alert or red herring? Fertil Steril 1993; 59:291-3

12. Duska LR, Wallach EE. Infertility, Ovulation Induction, and Epithclial Ovarian Cancer. Postgrad Obst Gynae 1996;16:1-7

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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.