Prevention of Multiple Pregnancy During Ovulation Induction

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Gonadotrophin ovulation induction is currently used for a heterogeneous group of ovulation disorders and unexplained infertility. In the United States it is reported that multiple pregnancy rates of greater than 30% occur as a result of ovulation induction, most commonly after controlled ovarian hyperstimulation and intrauterine insemination. Treatment strategies to reduce the incidence of multiple pregnancies on ovulation induction programs can be targeted to reducing multiple follicular development and subsequent ovulation by a more aggressive cancellation policy, follicle reduction by fine needle aspiration or conversion to IVF; or dealing with the problem of multiple gestation after it has occurred (i.e., multifetal pregnancy reduction). The procedures and abilities exist to resolve this problem. What is needed are appropriate treatment guidelines and well constructed trials to demonstrate that higher order multiple pregnancies can be substantially reduced and/or eliminated without compromising a couple's chances to conceive.

The aim of ovulation induction for anovulatory infertile women is to produce a single pre-ovulatory follicle so as to replicate the spontaneous chance of conception (20–30% per cycle). However for many patients the reality of ovulation induction is that multiple pre-ovulatory follicle development is the rule rather than the exception. Consequently the incidence of multiple gestations, especially higher order multiple gestation is a major concern.

An understanding of the clinical difficulties of initiating and monitoring folliculogenesis and subsequent induction of ovulation is necessary before appropriate treatment guidelines and recommendations can be adopted.

Ovulation Induction Indications

Ovulatory stimulants are currently utilised in a heterogeneous group of clinical conditions including ovulation disorders and unexplained infertility.

1. WHO Group I or hypo-gonadotrophic hypogonadism patients who present with amenorrhoea were the first group of patients treated with follicle stimulating hormone (FSH) to induce ovarian follicle growth, ovulation and pregnancy over 40 years ago (Gemzell et al., 1960).
2. WHO Group II or eugonadotrophic hypogonadism patients with anovulation treated with FSH were subsequently reported with regard to follicle growth, ovulation and pregnancy (Jacobs et al., 1975).
3. Unexplained infertility: As an alternative or prelude to in vitro fertilization and embryo transfer (IVF) FSH was administered to normally ovulating but infertile women to induce multiple co-dominant folliculogenesis prior to intrauterine insemination (Dodson & Haney, 1991).

Ovulatory Stimulants

Induction of ovulation is achieved either by manipulating the hypothalamic pituitary ovarian axis with Clomiphene citrate or by bypassing it with the use of FSH.

Clomiphene

Clomiphene is widely used and considered to be a "safe" ovulatory stimulant and is often administered as empirical therapy for unexplained infertility. However, multiple co-dominant pre-ovulatory follicle development is the rule rather than the exception with 25–70% of cycles developing two or more such follicles (O'Herlihy et al., 1980).

In appropriately selected patients, 80% of patients ovulate with 50% of those conceiving during a 6-month course of therapy. The pregnancy rate per induced ovulatory cycle is 15–20% (Gorlitsky et al., 1978). The multiple pregnancy rate is reported at 6–10%. Higher order multiple pregnancies occasionally occur.

The Merrell national laboratory follow up of 2369 pregnancies conceived with clomiphene (Asch & Greenblatt, 1976) revealed an overall multiple gestation rate of 7.9% (6.9% twins, 0.5% triplets, 0.3% quadruplets and 0.13% quintuplets). A set of sextuplets not included in the original census was subsequently reported.

Clomiphene should not be considered a universally safe or benign ovulatory stimulant.

Gonadotrophin Ovulation Induction (GOI) with FSH

As with Clomiphene the reality of ovulation induction is the development of multiple co-dominant follicles in over 50% of cycles (Insler & Potashnick, 1983). Practical problems with GOI include a variable "threshold" of FSH action between and within individual patient cycles, a change from no response to an exaggerated response with as little as a 30% increase in FSH dose, all monitoring "lags" activity at

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the FSH receptor site, and the low conversion rate of follicles ovulated to successful conception (Brown, 1978).

Conceptions on GOI cycles are influenced by patient selection, monitoring and treatment scheme in decreasing order of importance. The type of ovulatory disorder is important when considering conception rates. For patients with WHO Group I ovulation disorders pregnancy rates of up to 80% have been reported compared with 20–30% per cycle in WHO. Group II anovulatory patients. The same discrepancy is seen with cumulative pregnancy rates. Cumulative pregnancy rates of greater than 90% are reported in Group I patients after six cycles of treatment compared with Group II patients requiring 12 cycles of therapy to reach 60% cumulative pregnancy rate (Haning, 1982; Healy et al., 1980; Thompson & Hansen, 1970).

Monitoring of Ovulation Induction

Monitoring follicular growth and development involves measuring oestradiol production and or ultrasonic measurement of follicle development. The wide range of normal values for both these modalities means that they should not be relied upon to the exclusion of other modalities.

The oestrogen assay either in urine or blood may not be helpful in view of the wide range of normal values and are not predictive for multiple pregnancy (Haning, 1982). Prior to the widespread use of ultrasound monitoring there were some notable failures, with higher order multiple pregnancies occurring with oestrogen levels consistent with a single dominant follicle developing.

The use of ultrasound, with or in place of oestrogen monitoring, has improved the accuracy of ovulation induction (Yee & Rosen, 1990). Ultrasound observations and assumptions are based on spontaneous follicular observations which include: two dominant follicles observed in 21% of spontaneous cycles; maximum mean follicular development prior to ovulation of 20–24 mm (range 14–28); pregnancy uncommon if follicle less than 17 mm at ovulation; and linear follicle growth of 2–3 mm/day in the late follicular phase (Randall & Templeton, 1991). Extrapolation of these observations to multiple follicular development in GOI guides clinical decision making with regard to initiation of ovulation.

There are no clear guidelines or consensus as to when to induce ovulation with guidelines ranging from 3 or less follicles greater than 14 mm in size to 7 or less follicles greater than 16 mm in size. The tolerance for induction of ovulation with multiple follicles being present relates to the follicle size and the probability of ovulation. Silverberg et al. (1990) assessed the probability of ovulation based on the size of the follicle at the time of the HCG trigger for ovulation. Ovulation occurred at frequencies of 0.5% for follicles less than 14 mm, 72% for follicles 17–18 mm and 95% for follicles greater than 20 mm.

Controlled Ovarian Hyperstimulation: Intrauterine Insemination (COH.IUI)

The widespread use of COH IUI has resulted in an epidemic of multiple pregnancies. It appears that, where COH IUI is widely practiced along with IVF, that infertile couples are at a significantly greater risk of high order multiple pregnancy from COH IUI, than they are from IVF.

In a review of their clinical practice Gleicher et al. (2000) reported on pregnancy after COH.IUI in 3137 completed cycles. They reported a 14% clinical intrauterine pregnancy rate of which 71% were singletons, 22% twins, 5% triplets, 2.3% quadruplets, 1.1% quintuplets and 2% sextuplets. Cancellation of COH was strongly recommended if six or more follicles ≥ 16 mm in diameter on ultrasound were noted and oestradiol levels were greater than 9200pm/l. Cancellation was suggested if four or more follicles equal to or greater than 16 mm in diameter and oestradiol levels were greater than 7300 pmol/l. It should be hardly surprising that on occasion higher order multiple pregnancies occurred in this group. The chance of a singleton live birth/cycle commenced was 6% in this report.

Predictors of a higher order multiple pregnancy were, not surprisingly, younger age, increasing total number of follicles (> 6) and increasing serum oestradiol concentration (> 5000 pmol/l).

In contrast, Healey et al. (2003) reported a 6% singleton live birth per cycle commenced (510 cycles) of COH IUI with guidelines of ovulation triggering at follicle size of 14 mm and cancellation of the treatment cycle if more than 3 follicles greater than 14 mm developed. Of the pregnancies reported, 20% were twins and 2% triplets.

Current treatment of COH IUI results in a low chance of success per cycle started but when it is successful there is a significant risk of a twin or higher order multiple gestation.

Reducing Multiple Pregnancies

Strategies to reduce the incidence of multiple pregnancies would include reducing multiple follicular development or dealing with the problem when it occurs with procedures such as multifetal pregnancy reduction (Evans et al., 1994).

In view of the inherent difficulties of avoiding multiple co-dominant follicular development, other strategies are necessary to avoid multiple pregnancies occurring after multiple ovulations. A more aggressive policy of treatment cancellation if more than 3 pre-ovulatory follicles develop would reduce the incidence of high order multiple pregnancy but is unlikely to occur given the lack of such widespread guidelines with the dimensions of the problem being known for some time. Fine needle transvaginal ultrasound guided aspiration of excessive pre-ovulatory follicles is possible so as to not abandon the treatment cycle. The expertise and equipment to perform this are readily available in IVF units, which are often run in conjunction with the above treatment programs. Finally, the treatment when excessive could be converted to that of IVF with embryo transfer to limit the number of embryos reaching the uterine cavity.

Conclusion

Appropriate treatment guidelines based on well-constructed clinical trials are needed to address the issue and problem of multiple and especially high order multiple pregnancies. Treatments that are ineffective or dangerous should be modified or abandoned.

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