INDUCTION OF OVULATION BY GONADOTROPHIN

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SYNOPSIS

Between January 1975 to July 1977, 17 infertile patients were treated with gonadotrophins. Forty treatment cycles were given, 12 with human menopausal gonadotrophin and 28 with human pituitary gonadotrophin. Ovulation rate was 87.5% and pregnancy rate 58.8%. The mean number of treatment cycle per patient was 2.3, and the mean number of treatment cycle per pregnancy was 3.3. Individualized treatment schedule was adopted as considerable variability of ovarian response was noted between patient to patient and from cycle to cycle. Plasma oestradiol-17$\beta$was used in monitoring ovarian response. Cervical mucus findings could be misleading. No multiple pregnancy and severe hyperstimulation syndrome were encountered in our series. Six healthy female infants have been delivered. Close daily monitoring with laboratory support ensures safety and effectiveness of gonadotrophin therapy.

INTRODUCTION

Since the first report by Gemzell and co-workers in 1958, human gonadotrophins have been effectively and widely used in the treatment of infertility due to anovulation. Extensive experience of this treatment have been reported by Van de Wiele and Turksoy (1965), Kase et al (1968), Roland (1969) and Australian Human Pituitary Advisory Committee (1976). In Singapore, this form of therapy became available only in the University Department of Obstetrics and Gynaecology since 1975. The paper reports our preliminary experience.

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MATERIALS AND METHODS

A. Patients

Between January 1975 to July 1977, 17 patients were treated. All the patients had persistent anovulation and were attending the infertility clinic at the University Department of Obstetrics and Gynaecology, Kandang Kerbau Hospital, having been through the preliminary investigations in this clinic. They included basal body temperature chart, laparoscopy, hydrotubation and/or hysterosalpingogram, uterine curettage and/or ovarian biopsy. All the husbands had a seminal analysis and all the patients had previously been treated with clomiphene without success.

B. Gonadotrophins

Human pituitary gonadotrophin (HPG) was prepared by extraction from cadeveric pituitaries. Human manopausal gonadotrophin (HMG) and human chorionic gonadotrophin (HCG) were obtained from Organon Co.

C. Hormones Assayed

Plasma oestradiol-17β, plasma progesterone and B subunit of HCG were measured by radioimmunoassay (Chew and Ratnam 1976a, 1976b and Salmon et al, 1976).

D. Regime of Treatment

The patient was seen daily. Basal body temperature was charted and cervical mucus assessed according to the amount, clarity, spinnbarkeit and fern ing pattern. Heparinised venous blood was taken and plasma oestradiol-17β estimated and the result was available the following morning. HPG was given at a dose of 60–70 IU on alternate day for 3 days after which the dose was either maintained or increased daily according to the response of plasma oestradiol-17β level. When the level of about 1000 pg/ml or above was reached, HCG at 6000 IU was given followed by 3000 IU the next day. Postcoital test was performed for 4 days after the initial dose of HCG was given. Additional doses of HCG were given to help maintain the corpus luteum. A similar regime was employed for HMG.

RESULTS

Table I summarises the results of gonadotrophin therapy.

TABLE I: Results of Gonadotrophin Therapy

Ovulation rate	87.5%
Pregnancy rate	58.8%
Abortion rate	33.3%
Mean number of treatment Cycle per patient	2.3
Mean number of treatment Cycle per pregnancy	3.3

A. Ovulation

Forty courses were given, 12 with HMG and 28 with HPG. Ovulation was induced in 35 courses. The evidence for this is based on the number of pregnancy, the appearance of luteal phase values of plasma progesterone (above 10 ng/ml) and a rise of basal body temperature when HCG was given to a patient whose plasma oestradiol-17β had reached a satisfactory level.

The total dosage per cycle required to achieve ovulatory level of plasma oestradiol-17β varied from 1575 to 4125 IU for HMG, and 400 to 820 IU for HPG. The response to gonadotrophin in any one patient varied considerably from cycle to cycle.

B. Cervical Mucus

Lack of response of endocervical gland to oestrogen was noted in 6 of the 35 courses when ovulation occurred. The cervical mucus remained thick, scanty, turbid with negative ferning inspite of high plasma oestradiol-17β levels of 1000 pg/ml and above. Disparity between cervical mucus and plasma oestrogen was also noted in 2 of the 5 non-responsive cycles. In this case, low oestrogen was associated with abundant clear mucus with ferning between 2+ to 3+.

C. Pregnancy

Twelve pregnancies occurred in 17 patients, with one patient being pregnant twice. Two pregnancies occurred in the HMG group and 10 in the HPG group (Table II).

TABLE II: Number of Pregnancy in Relation to Type of Gonadotrophin Used

	Treatment cycle	Pregnancy	Treatment cycle per pregnancy
HMG	12	2	6
HPG	28	10	2.8
Total	40	12	3.3

In the HMG group, one had threatened abortion which had settled and the pregnancy is currently continuing. The other patient aborted a single foetus weighing 600 grams at 24 weeks gestation.

In the HPG group, 2 had spontaneous abortions in the first trimester, one had missed abortion and one had molar pregnancy. The remaining 6 pregnancies were all singleton and healthy female babies were delivered at term, 1 spontaneously and 5 by lower segment caesarean section.

D. Ovarian Hyperstimulation

Enlargement of ovaries was observed only after HCG was given. Ovaries were palpable in 14 of the 35 ovulatory cycles. They varied from 6 cm to 24 cm in diameter. Only 1 patient required hospitalization for a day for abdominal pain. None of the patients had ascites or hypotension.

DISCUSSION

Ovulation induction of gonadotrophin is one of the major advances in the treatment of infertility. However, such therapy is not a panacea and can be associated with serious morbidity and even mortality. In Singapore, this form of therapy has been available since 1975 and our experience so far has been encouraging. The ovulatory treatment cycles and the pregnancy rates in our patients compared favourably with most series reported in the literature.

Our study as well as many others, have shown that patients vary greatly in their response to gonadotrophins and in any one patient, the response varies considerably from cycle to cycle. Several treatment schedules have been proposed. However, we found the individualized treatment schedule according to the ovarian response to be the most satisfactory one. In this way, follicular steroidogenesis as well as other follicular maturation processes can be built up sufficiently slowly for successful ovulation to occur. Too rapid a rise in plasma oestradiol-17β was associated with failure to achieve ovulation. In our study of the normal menstrual cycle (Salmon et al, 1976) the late proliferative phases rise of plasma oestradiol-17β started 6 days before the mid-cycle peak. It is likely that this represents the rapid growth spurts of a single maturing Graffian follicle. In the 12 pregnant cycles studied, the time taken for plasma oestradiol-17β level to rise from basal level to 1000 pg/ml or more varied from 4 to 8 days.

In gonadotrophin therapy, monitoring the ovarian response by hormone assay cannot be overemphasised. A particular virtue of plasma assays as opposed to the urinary measurements lies in the dose control which the former makes possible. The plasma responses were quicker and relatively much larger so that one is seldom in doubt what stage of ovarian responses has currently been reached (Shaaban and Klopper, 1973). Clinical parameter using cervical mucus as a measure of ovarian response can be misleading. Our study showed that in both ovulatory and anovulatory treatment cycles, discrepancy between plasma oestrogen and cervical mucus findings was not uncommon. Furthermore, response of endocervical glands can change from cycle to cycle in any one patient.

Our 33% abortion rate is in accordance with many other studies. The cause of the high rate of abortion is not well understood although Brown et al (1969) suggested that abnormal steroid pattern might be responsible.

The predominance of girls in children borne after gonadotrophin therapy were noted by many workers (Hack et alm 1970; Caspi et al, 1976). In this series, all the babies borne were girls. The reason for altered sex ratio is uncertain.

Although ovarian enlargement was present in about 40% of ovulatory cycles, there was no severe hyperstimulation syndrome. This is probably attributed to the close daily monitoring of the patient, which though tedious, will ensure safety and effectiveness of gonadotrophin therapy.

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