GONADOTROPINS FOR INDUCTION OF OVULATION

By

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SUMMARY

Induction of ovulation employing hMG/hCG and pure FSH/LCG is described in this communication. Follicular sonography coupled with BBT recording and cervical mucus study has been the method of monitoring employed. With this monitoring protocol we observe excellent results for the hypogonadotropic-hypogonadal subjects (estrogen deficient normoprolactinemic subjects). The same monitoring protocol appears to be clinically acceptable and practicable for the PCOD subjects who had induced ovulation employing gonadotropins. The pregnancy rate is attractive and incidence of ovarian hyperstimulation is less. We feel that pure FSH is a more acceptable and safe alternative to hMG for subjects with PCOD. However, we are of the opinion that the PCOD subjects who are clomiphene resistant should be given a fair trial with laparoscopy ovarian follicular puncture/wedge biopsy before considering them for gonadotropin therapy.

Introduction

Ovulation induction with pharmacologic agents has been usually reserved for the treatment of infertile women with oligomenorrhoea or secondary amenorrhoea not secondary to ovarian failure. Usually gonadotropin treatment is considered a 'last hope' drug. Human gonadotropins are among the most successful medications for induction of ovulation; however, their use is complex and the potential complications are significant. With proper patient selection and optimal monitoring facilities gonadotropins aim at a very high pregnancy rate.

There are usually two groups of anovulatory infertile subjects recruited for gonadotropin induction of ovulation: (i) Generally, hypogonadotropic hypogonadal patients are the most susceptible to gonadotropin therapy. These patients have low basal gonadotropin levels and lack endogenous estrogenic activity. Most of these patients have hypothalamic hypogonadotropic hypogonadism and normal serum prolactin levels. (ii) Women with low normal or normal gonadotropins levels and evidence of endogenous estrogenic activity, and they may even have abnormally high LH levels with low normal FSH values; Most of the patients have hypothalamic-pituitary dysfunction and the PCOD syndrome, and they are classically the subjects who have failed to respond to clomiphene citrate and/or wedge resection.

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Patient selection and pretreatment evaluation

Group I subjects: The 'estrogen deficient' (hypo-estrogenic) groups, usually present with secondary amenorrhoea and clinical examination reveals a normal looking female with no hirsuitism, obesity or galactorrhoea. Pelvic examination indicates hypoestrogenism as evidenced by uterine size, nature of cervical secretion and texture of vaginal mucosa. Progesterone challenge (injection of 75 mg of plain progesterone) is invariably negative (no withdrawal bleeding) further documenting the hypoestrogenic state. At this stage primary gonadal failure including resistant ovary syndrome is excluded by estimation of serum FSH level. A high level (above 25 mIU) of FSH identifies the primary gonadal failure group and a normal or low value diagnosed the secondary gonadal failure. The latter group of estrogen-deficient subjects have normal but non-functioning (sleeping) ovaries due to the hypogonadotropic state, and are the most suited candidates for induced ovulation by employing gonadotropins, provided a hypothalamic-pituitary lesion such as a prolactinoma is excluded. Hence a routine study of sella turcica and serum prolactin estimations are mandatory before deciding on gonadotropin regimen.

Group II subjects are the oligomenorrhoeic subjects who are estrogenised and respond promptly to progesterone challenge. These subjects, quite often the PCOD group, are relatively obese and not infrequently manifest evidence of hirsuitism. They have been essentially treated with clomiphene citrate (CC), CC and dexamethasone, CC nd hCG, CC, bromocriptine and hCG, and sometimes ovarian wedge resection by the classical method or through laparoscopy. Since all these therapeutic modalities have failed to achieve ovulation they have been selected for gonadotropin therapy.

In either group, a pretreatment study included a thorough male factor evaluation, and an endocrine evaluation of the female partner. Unless clinically indicated, a routine HSG or diagnostic laparoscopy verification of tubal patency was not performed.

Extensive counselling of the couple was mandatory, particularly related to the cost of the drug, the protracted course of therapy, need for regular sonographic monitoring, the importance of the couple's participation in the programme, the importance of maintaining BBT chart and the possible ovarian hyperstimulation (particularly in the normo-estrogenic PCOD subjects). Group II subjects (normo-estrogenic) are also given the option between surgical induction (laparoscopic follicular puncture-aspiration of the cysts) and gonadotropin therapy, and the patient was allowed to indicate her preference. She was also told that she could be crossed over to either treatment any time. We have found patients quite often preferring laparoscopic follicular puncture over gonadotropin therapy, and we also feel fair trial with laparoscopic follicular puncture followed by CC therapy should be given before resorting to gonadotropins.

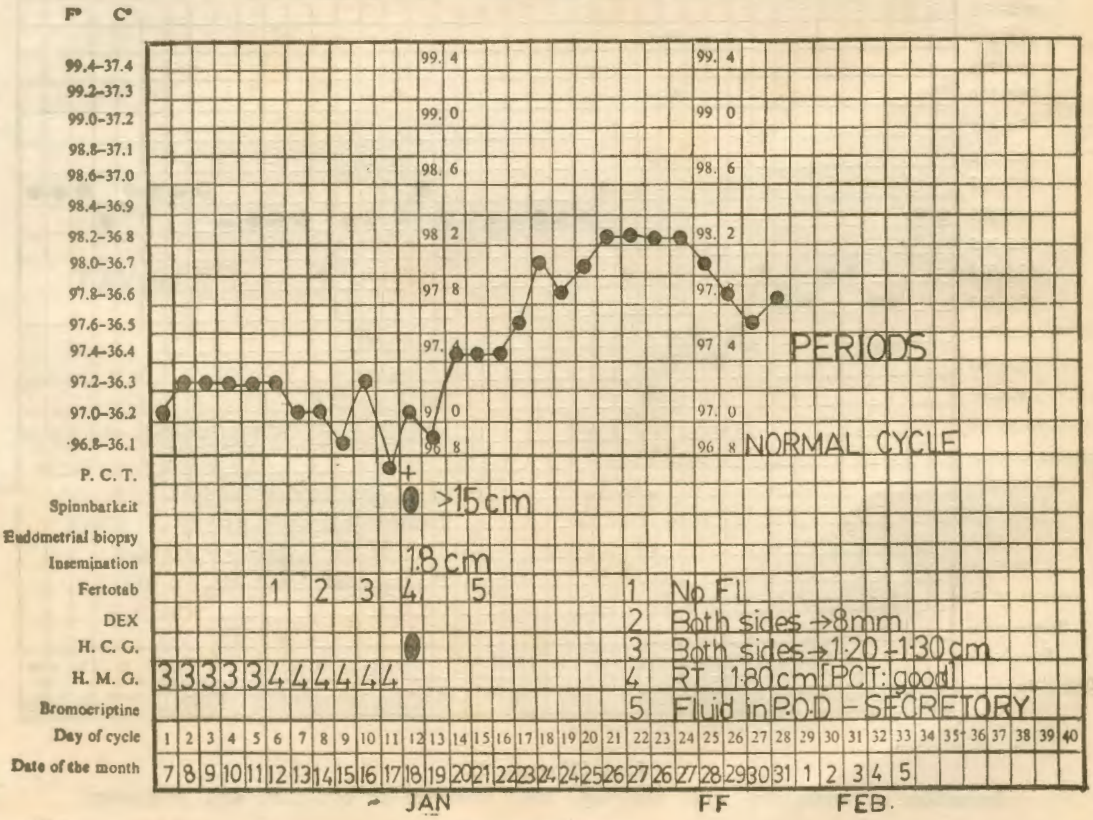
Treatment Protocol

In all patients, treatment with gonadotropins was begun following spontaneous menstruation or induced withdrawal bleeding employing progesterone or estrogen-progestin combination. The gonadotropin preparations employed included: (i) human menopausal gonadotropin (hMG)—FSH 75 i.u. and LH 75 i.u.; (ii) human

urinary FSH (pure FSH)—FSH 75 i.u., and LH less than 1 mIU; and (iii) hCG—5000 i.u. (imitating the LH activity). BBT chart, cervical mucus study and sonographic follicular and endometrial study were the methods of monitoring employed for adjusting the dose of gonadotropins and time of administration of hCG.

Group I: Subjects in this group were essentially hypogonadotropic and hence hypoestrogenic. They tolerated, and indeed needed an enhanced dose of hMG, and sometimes greater duration of treatment to obtain the ovulatory response from the hitherto unstimulated ovaries. On an average 1 to 3 ampules, and sometimes 4 ampules of hMG was given daily, beginning from the 2nd or 3rd day of menstruation. The drug was begun on a dose of 2 ampules per day, and the dose was adjusted depending on the size and number of developing follicles. It was observed that these subjects need on an average 8 to 10 days treatment to have atleast one follicle matured to 18 to 20 mm diameter and to have adequate secretion of cervical mucus. Usually not more than 2 follicles developed in these subjects except in one who had 4 pre-ovulatory follicles. Response to gonadotropin therapy was relatively quick and normal ovulatory response was achieved usually within 3 treatment cycles, except in one subject who took 12 treatment cycles.

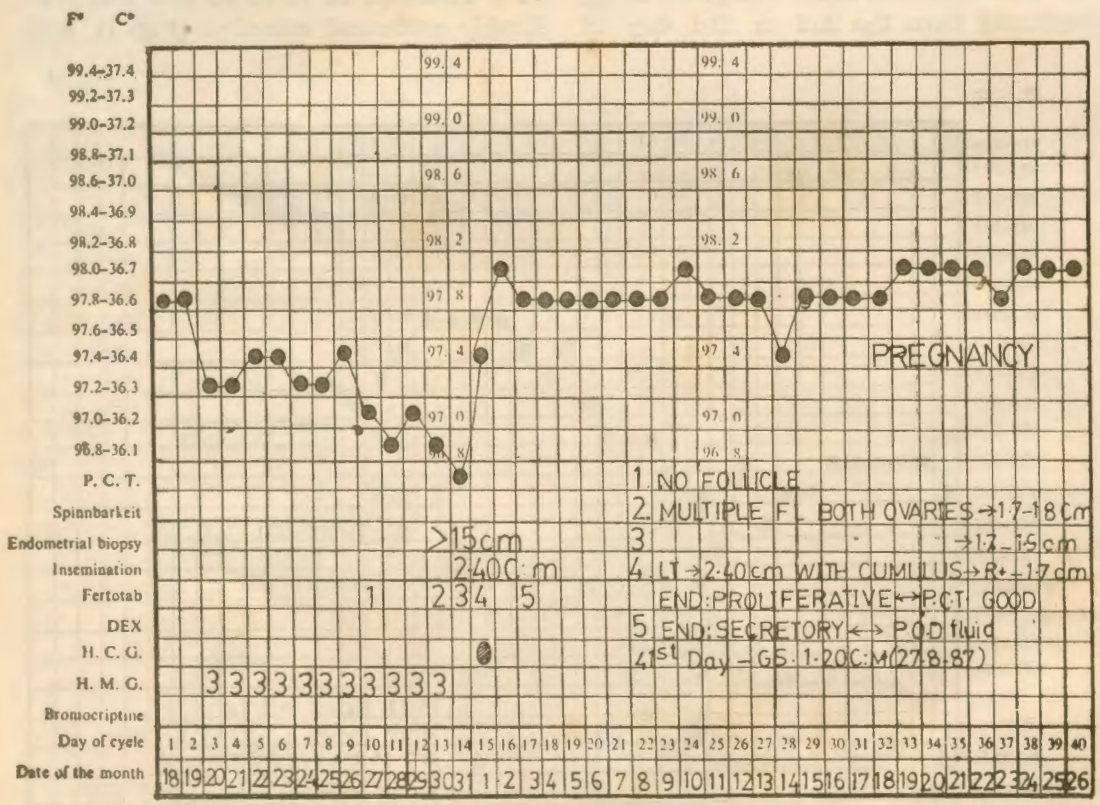
When the dominant follicle had reached a diameter of 18 to 22 mm and preferably evidenced cumulus (Fig. I), and



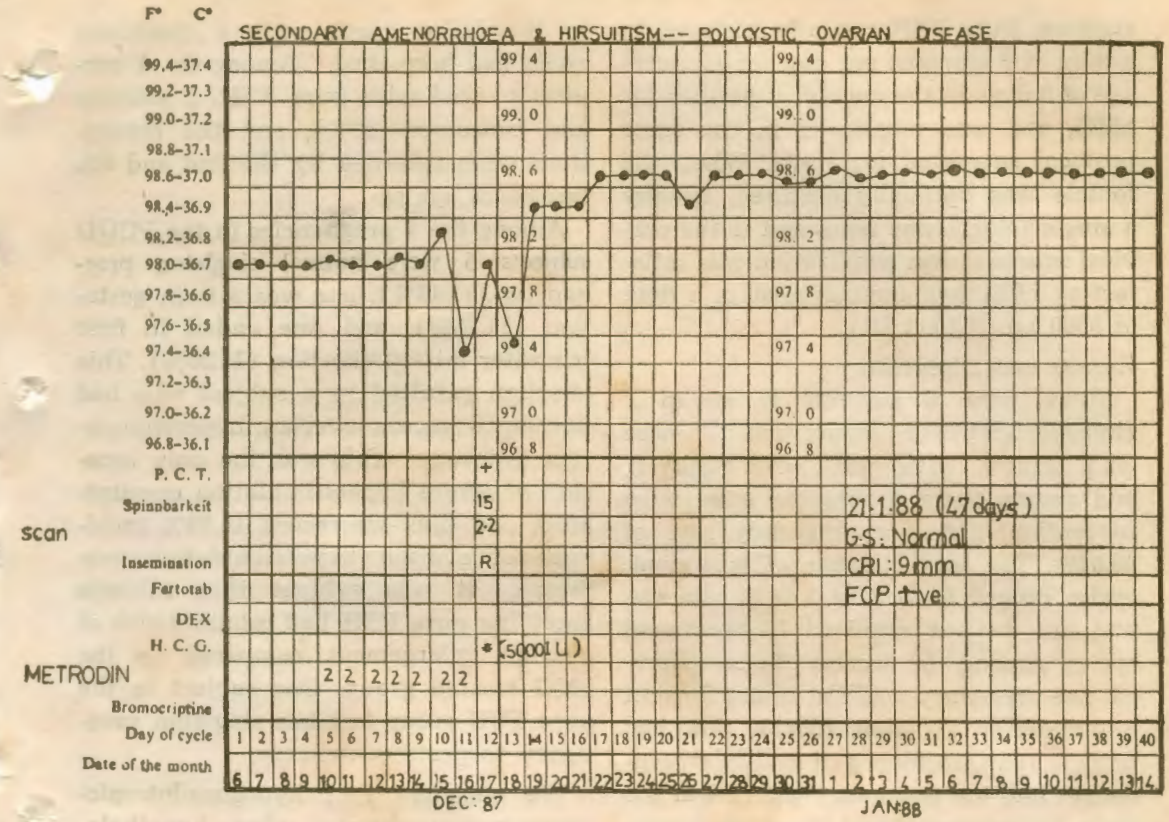
Line Diagram I
Induction of ovulation with hmg/hcg biphasic B.B.T. indicating ovulation.

when cervical mucus secretion was adequate and sperm penetration positive, hCG was administered. Follicular sonography is performed almost daily after the follicle had reached a diameter of 15 mm, and proliferative changes in the endometrium was also considered as an additional monitoring parameter. The dose of hCG employed was 5000 to 10,000 i.u. Sonography was repeated 48 hours after hCG administration to verify the occurrence of ovulation. Sonographic post-ovulatory changes include: (i) disappearance of the follicle, (ii) secretory changes in the endometrium, with a clear endometrial cavity demonstrated, and (iii) fluid in the POD (Fig. II). The BBT evidence of biphasic temperature pattern was taken as additional proof for ovulation (Chart I). The thermal nadir was usually observed to coincide with the optimally matured follicle which could be induced to ovulate by employing hCG.

A routine sonographic inspection was carried out around 10th post ovulatory day to collect the following informations: (1) evidence of hyperstimulation, in the form of multiple luteinized follicles, and (ii) presence of brightly echogenic secretory endometrium/decidua, which quite often prognosticated the possibility of conception (Fig. III). The BBT recording was continued, and sustained thermal rise coupled with amenorrhoea of 33



Line Diagram II
Induction of ovulation with bmg/lcg. BBT evidence of ovulation and pregnancy.



Line Diagram III
Induction of ovulation with Fsh/lcg. B.B.T. evidencing ovulation and pregnancy.

days or more was considered an urgent indication for sonographic evaluation of pregnancy (Fig. 4) and Chart II).

Group II: Subjects in this group were hypergonadotropic (high LH) and hence had stimulated ovaries, which were quite often polycystic. They were approached more cautiously with the drug, because they will be hyper-responsive to gonadotropins. Even with one ampule of hMG, given daily for 6 to 9 days they may go for hyperstimulation. We had employed 1 to 2 ampules of hMG given for 6 to 9 days, and quite often came across more than 2 follicles developing. The monitoring protocol was the same as described for group I subjects. However, the hCG dose employed for induction of follicular rupture was reduced to 5000 i.u., and the drug was withheld if more than 2 dominant follicles were located. Despite a very careful approach ovarian hyperstimulation chances were very high in this group of subjects.

To obviate the problem of ovarian hyperstimulation, we had employed 'pure FSH' for induction of follicular maturation. The logic was that these subjects were already circulating high LH and were deficient in FSH, and hence they should need only FSH support for optimal follicular maturation. After achieving adequate follicular maturation hCG was administered to induce follicular