INDUCTION OF OVULATION WITH GONADOTROPINS

by

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Since the first therapeutic use of human pituitary gonadotropins by Gemzell (1958) and of HMG by Lunenfeld (1962), it has been now well-established that human gonadotropins from these two sources followed by HCG can be used for induction of ovulation in suitable cases.

This report presents our results only on the use of HMG in a group of amenorrhoeic women.

There were three patients, two of primary amenorrhea and one of secondary amenorrhea. These were young women, between the age 26-31 years and infertility was the main motive for submitting them to this therapy.

A complete infertility and endocrine work-up was carried out on each patient. This included a basal temperature record, tubal patency test, endometrial biopsy, progestin withdrawal test, sex chromatin study and the determination of total gonadotropic activity, urinary 17 KS, 17 OHCS and thyroid function tests prior to initiation of therapy. All patients had an X-ray examination of skull to rule out pituitary tumours. No treatment was begun unless the male factor was considered normal.

Table I gives a detailed information on clinical data on each patient.

TABLE I

Clinical Data

Name & Age	Clinical Diagnosis	Uterus	Ovaries	Endometrium	Vaginal Cytology	Remarks
1. S. N. 31 yrs.	Pr. Amen.	Small	Not palpable	None	Atrophic smear	Secondary sex characters underdeveloped
2. D. A. 29 yrs.	Pr. Amen.	Small	Not palpable	Atrophic	Atrophic	Fairly well developed
3. B. Z. 26 yrs.	2° Amen.	Normal	Normal	Inactive prolif.	Intermediate group	Normally developed

Clinical Data (Contd.)

Patient	Gonadotrophins	17 ks	KGS	Progest withdrawal test	Response to estrogens	Clomid	Sex chromatin
1. S. N.	—ve	Low	Low	— ve	+	— ve	+
2. D. A.	+ at 20 — at 25	Normal	Normal	— ve	+	— ve	+
3. B. Z.	+ at 5 — at 10	Normal	Normal	+ ve	+	±	+

Assessment of Response: The response to treatment is manifested by ova-

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rian stimulation reflected by a number of changes, some indicating an estrogenic effect and others ovulation or progestational changes.

Table II describes the parameters evaluated for this purpose.

TABLE II

Criteria of Ovarian Response

Parameters	Indices of evaluation
1. Vaginal epithelium	Karyopyknotic index
2. Cervical mucus	Spinnbarkeit
	Fern test
	Volume of mucus
3. Endometrium	Proliferative-Secretory changes
4. Basal temperature	Biphasic changes
5. Urinary estrogens	Increasing levels
6. Urinary pregnanediol	< 2 mg/24 hrs.

Daily Changes in Vaginal Cytology: The Kariyopyknotic Index (K. P. I.) and luteal effect were used to assess ovarian response to gonadotropin therapy from day to day. The rise in KPI points to an increased estrogen effect on the vaginal epithelium. This increase along with changes in cervical mucus could be used to monitor the FSH treatment. With increasing estrogen excretion from the growing follicles, the cervical mucus increases in volume, decreases in viscosity and shows the phenomenon of Spinnbarkeit and ferning or arborization pattern.

Secretory changes in the endometrium would indicate the occurrence of ovulation and corpora lutea formation in a cycle, but cannot be carried out in each and every cycle. Basal temperature record during gonadotropin therapy is very important, as a clear shift in the temperature gives an indication of the day of ovulation and also indicates the duration of the luteal phase.

Measurements of urinary estrogens could be ideally used as a guide for follicular maturation in monitoring the dosage and duration of gonadotropin therapy. However, this could be useful only where laboratory facilities are sufficiently good to furnish rapid results within a day.

The urinary pregnanediol estimation during the later part of the cycle is used as an additional evidence for formation of corpus luteum and for the progress of pregnancy.

Method of Therapy: In this study HMG used was supplied as Pergonal in ampoules containing 75 I.U. of FSH and about 75 I.U. of LH. This LH component in HMG is insufficient to produce ovulation, but is probably necessary to produce the desired follicular growth and maturation. The HCG used was Pregnyl (Organon) containing 1,500 I.U. per ampoule.

The principle of this therapeutic regime is to imitate the physiological sequential release of FSH and LH in a normal ovulatory cycle. HMG was therefore given initially to produce adequate follicular maturation over a period of 8-14 days and then HCG was given to trigger ovulation at a dose of 5,000-9,000 I.U. over one or more days. If pregnancy does not occur, a withdrawl bleeding may be expected 12-14 days after HCG administration.

While the administration of HCG is fairly well-standardized, the duration, dosage and regime of HMG is subject to considerable individual variation.

In our study HMG was initially given daily at a dosage of 1 or 2 ampoules till adequate follicular maturation was achieved. This can be assessed by rapid estrogen assays indicating an increase of estrogen to a level of about 50 μgm/per 24 hours or a 3 plus cervical score and 60-80% KPI of vaginal smears.

TABLE III

Corrrelation between the Intensity of Therapy and Response of Cervical Mucus

	HMG Therapy	Response of cervical mucus +++
B.J. 1st Cycle	15 x 75 I.U.	++ to +++
2nd „	16 x 75 I.U.	++ to +++
3rd „	16 x 75 I.U.	+++
S.N. 3rd „	29 x 75 I.U.	+++
4th „	30 & 39 x 75 I.U.	+++
5th „	30 x 75 I.U.	+++
6th „	30 x 75 I.U.	+++

Table III shows a correlation between the intensity of HMG therapy and a 3 plus response of cervical mucus in 2 patients over 7 cycles. In our limited experience, the same amount of FSH dose seemed to produce the desired response in different cycles in the same patient. (Crooke, 1970). Once it was known that a certain dose of HMG was enough for a patient to produce adequate follicular maturation, one may divide this dose and give it on alternate days over 3-6 days followed by HCG as already described.

Results of HMG Treatment: Table IV

TABLE IV

Results of HMG + HCG Therapy in Different Cycles

Patient	Cycles	Total HMG in days	Dose of HCG	Day of HCG Therapy	Ovulation	Side-Effects
B. Z.	1st	21 AMP. (15)*	3,000 x 3	13th	+	—
	2nd	19 AMP. (11)	3,000 x 3	9th	+	—
	3rd	20 AMP. (11)	3,000 x 3	9th	+	++
D. A.	1st	32 AMP. (8)			No Ovarian response	
S. N.	1st	10 AMP. (10)	4,500 x 3	11th	—	— (M.P.)
	2nd	25 AMP. (14)	4,500 x 3	12th	+	++
	3rd	28 AMP. (20)	CLOMID	-	—	— (M.P.)
	4th	41 AMP. (15)	9,000 + 5,000	15th	+	++
	5th	35 AMP. (7)	4,500 + 1,500	14th	+	+
	6th	30 AMP. (3)	5,000 + 1,500	9th	+ Preg.	—

* Figures in brackets indicate number of days on which therapy was given.

shows the results of HMG + HCG therapy in individual cycles.

Patient B. Z., a case of secondary amenorrhea, was given 1-2 ampoules of HMG daily followed by 3,000 I.U. of HCG given for 3 days successively. The cycles were considered ovulatory in all cases, but there was no pregnancy. The patient complained of pain in the lower abdomen and developed enlarged ovaries during the 3rd cycle.

The second patient D. A., a case of primary amenorrhea, was given a total of 32 ampoules on 8 alternate days but showed no evidence of follicular maturation. This was a case who had high endogenous gonadotropins to start with.

In contrast, the responses of patient S. N., another case of primary amenorrhea who had negative urinary gonadotropins, was more favourable.

The first cycle was a test cycle which was followed by menstrual period, but there was no ovulation. The second cycle where 25 ampoules of HMG was given, was found to be ovulatory, but there were some side-effects. The third cycle HMG produced adequate follicular response, but instead of HCG, Clomid was given, but there was no ovulation.

In the next three cycles, dosage of HMG was varied ranging from 30-41 ampoules and so was the number of days of administration. Instead of a daily injection, larger doses were given divided over 7 and 3 alternate days in the 5th and 6th cycles. HCG dosage was almost the same, but the day of administration was varied depending on individual judgement and patient response.

The results of therapy can be classified according to the type of response as shown in Table V.

TABLE V

Results of HMG Therapy

Type of response	No. of cycles
1. Ovulation and conception	1
2. Ovulation without Conception	6
3. Ovarian stimulation without ovulation	2
4. No ovarian response	1

Table VI correlates the results of therapy to the respective clinical diagnosis.

In the group of primary amenorrhea, 5 out of 7 treated cycles were ovulatory and there was one pregnancy. There was only one case of secondary amenorrhea and in this case all the 3 treated cycles were ovulatory.

Table VII shows correlation between therapeutic success and duration of HMG therapy. The number of total cycles is not large in our study and hence it is difficult

TABLE VI

Types of Cases and Overall Results of Therapy with Gonadotrophins

Diagnosis	No. of cases	No. of cycles	Ovulatory Cycles	No. of Pregnancies
Prim. Amenorrhoea	2	7	5	1
Sec. Amenorrhoea	1	3	3	

TABLE VII

Correlation between Therapeutic Success and Duration of HMG Therapy

Days	No. of cycles	Therapeutic Response		
		+ ve	— ve	Pregnancy
<10	3	2	1	1
11-15	6	5	1	-
16-20	1	1	-	-
Total	10	8	2	1

to deduce any conclusions, but the general trend today is towards reducing the duration of HMG therapy. It should preferably be given over a ten days period.

Side-effects and Complication of Treatment

All side-effects and complications are a result of overstimulation of the ovaries. The result is either multiple pregnancy or a rapid ovarian enlargement with peritoneal effusion and haemorrhage known as hyperstimulation syndrome. We have had no multiple pregnancy so far. The hyperstimulation syndrome was encountered in 4 out of 10 treated cycles shown in Table VIII. It may be divided into three types, mild, moderate and severe. It consisted of low abdominal pain, nausea, sometimes diarrhoea and the ovaries were found to be enlarged, cystic and tender. In the severest form which we did not encounter, it could be complicated by ascites, pleural effusion, changes in blood volume, thrombosis, etc. Symptoms first appear within a few days after HCG administration. They usually subside in about a week's time with conservative line of treatment. Rarely is a laparotomy indicated for evacuation of intraperitoneal effusions.

TABLE VIII

Side-effects

No. of treated cycles	Side-effects
10	4

Fig. I shows the response of patient B. Z., a case of secondary amenorrhea, to HMG administration during her 3rd cycle.

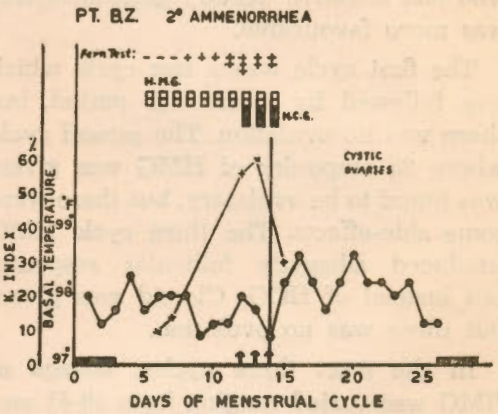

Fig. 1

Patient B. Z. (Secondary Amenorrhea) Changes in Karyopyknotic Index (x—x) cervical mucus score and basal temperature (o o) in relation to treatment schedule.

Patient B. Z: 3rd Cycle: HMG therapy was started on the 5th day. On the 12th day when cervical mucus showed +++ response HCG 4,500 I.U. were given along with HMG for 3 days and the patient was asked to have sexual relations on all these days. Ovulation seemed to

have occurred on day 14. But there was no pregnancy, and the patient complained of pain in the abdomen and cystic ovaries the size of a small orange on one side was palpated. The patient had menses on 26th day. The post-ovulatory phase was of 12 days duration. It took much less of FSH, only 14 ampoules of HMG to stimulate the ovarian follicles to secrete enough estrogen to give a +++ response in the cervical mucus.

In comparison, the next patient S. N., a case of primary amenorrhea with negative gonadotropin values in her urine was more resistant.

Patient S. N.: 4th Cycle. Fig. II: Here HMG was administered for 15 days daily. The cervical mucus showed maximum response on day 12 after 30 ampoules, but as the KPI in vaginal smears had not gone up adequately, we waited for 3 more days before administering HCG. In this case ovulation did occur but there was no pregnancy and the patient

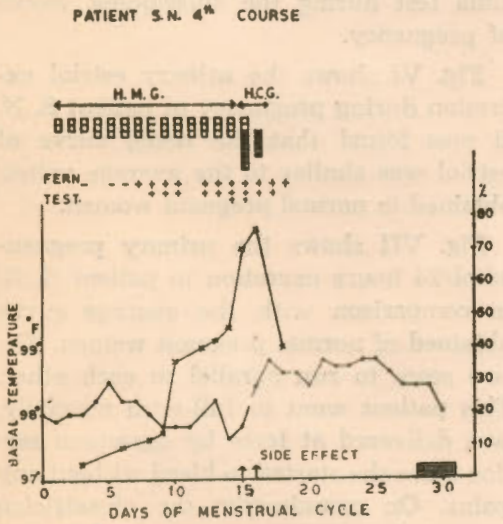

Fig. 2

Patient S. N. (Primary amenorrhea) Response to gonadotrophin therapy during the 4th course of treatment.

complained of some side-effects like pain in the abdomen, during her luteal phase.

Patient S. N.: 5th Cycle Fig. III: In this cycle HMG was administered on alternate days, 5 ampoules at a time. On

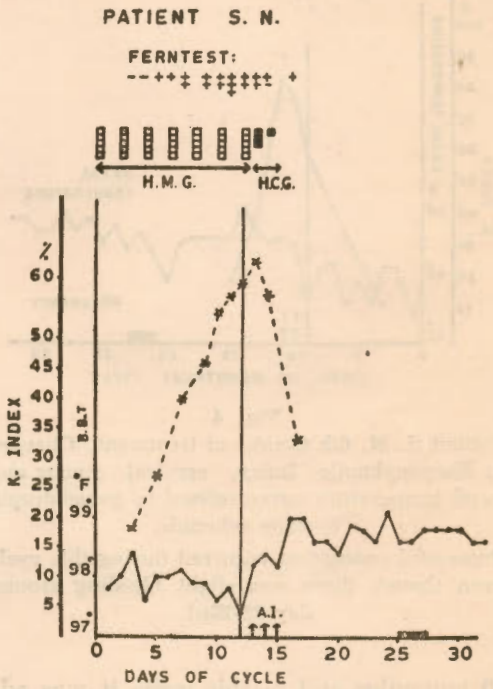

Fig. 3

Patient S. N. (5th course of treatment). The basal temperature shift occurred before administration of HCG.

day 10, i.e., after 30 ampoules, a 3 plus response of cervical mucus was noted but we waited, perhaps a day too long and in this case, the temperature already showed a shift when HCG was administered. Artificial insemination (AI) was done for 3 days starting on the day when HCG was administered, but it was perhaps too late. The cycle was ovulatory and the menstrual period occurred, 14 days after shift of B. B. T.

Patient S. N.: 6th Cycle. Fig. IV: By now it was realized that the optimum ovulatory dose for this patient was about

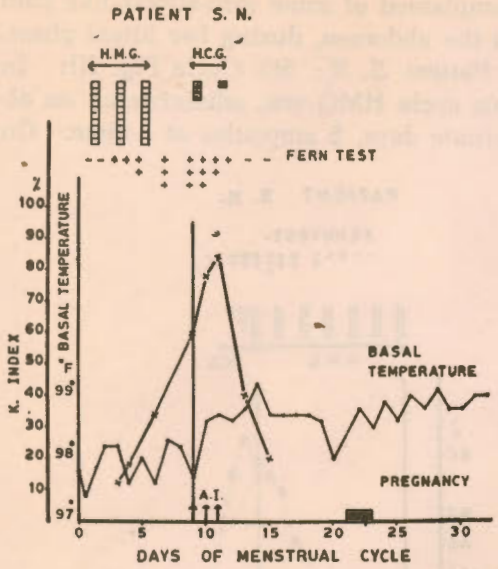

Fig. 4

Patient S. N. 6th Course of treatment. Changes in Karyopyknotic Index, cervical mucus and basal temperature curve related to gonadotropin therapy schedule.

Successful conception occurred during this cycle even though there was slight bleeding around day 22-23rd.

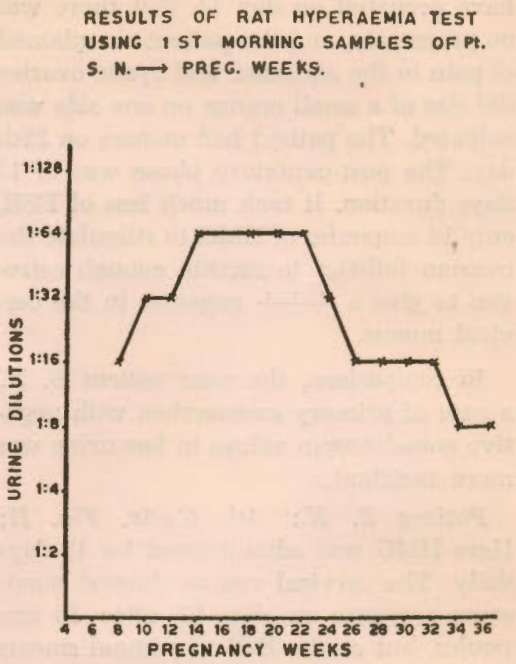

Fig. 5

Results of semi-quantitative test for HCG in urine throughout pregnancy in patient S.N.

30 ampoules and in this cycle it was administered in 3 divided doses on alternate days. The maximum cervical mucus response was obtained on day 7, but we waited for two more days, the cervical mucus response of +++ continued and on day 9, AI was done and 5,000 I.U. HCG was administered. The AI was continued for two more days and HCG repeated on day 11. Ovulation occurred on day 9 and there was a good BBT shift. There was slight bleeding on 21st and 22nd day. The temperature after a slight dip continued to be maintained at a high level. Immunological pregnancy test was done on morning urine a week later and found to be positive.

HCG determination by rat ovarian hyperemia test during the subsequent weeks of pregnancy.

Fig. V shows the semi-quantitative

Fig. VI shows the urinary estriol excretion during pregnancy of patient S. N. It was found that the rising curve of estriol was similar to the average values obtained in normal pregnant women.

Fig. VII shows the urinary pregnanediol/24 hours excretion in patient S. N. in comparison with the average curve obtained of normal pregnant women. The two seem to run parallel to each other. This patient went to full-term normally, was delivered at term by caesarean section since she started to bleed without any pains. On examination the obstetrician suspected a placenta praevia and operated. A full-term normal baby girl was delivered weighing 6½ lbs. The baby was perfectly normal.

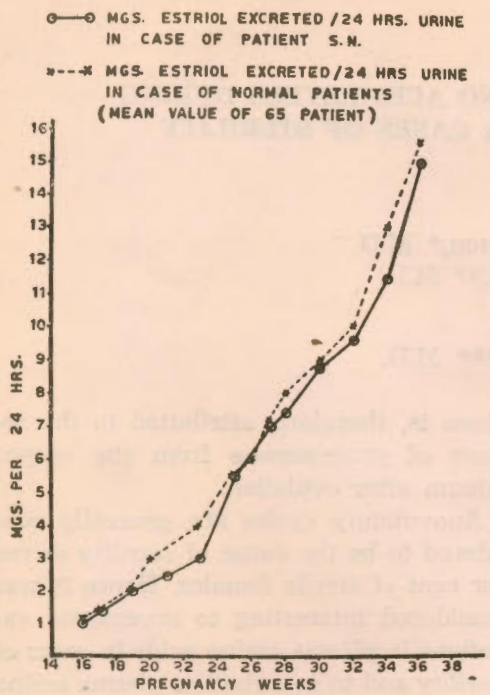

Fig. 6

Excretion pattern of urinary estriol during pregnancy of patient S. N. in comparison to mean curve obtained in normal pregnancy.

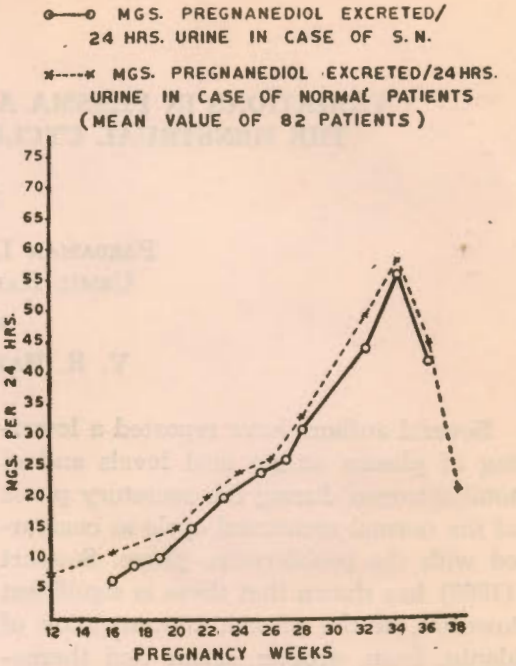

Fig. 7

Excretion pattern of urinary pregnane diol of patient S. N. in comparison to a mean curve obtained in normal pregnancy.

In conclusion, treatment with gonadotropins is remarkably effective in a certain group of patients. Hence the selection is very important. It can be very dangerous unless the dosage is monitored by daily laboratory tests and clinical evaluation of the patient. The treatment should be undertaken only at centres where full endocrine facilities exist and by people experienced with this therapeutic regime.

Acknowledgements

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