

INDUCTION OF OVULATION WITH HUMAN MENOPAUSAL GONADOTROPIN; WITH SPECIAL REFERENCE TO OVARIAN HYPERSTIMULATION SYNDROME AND HORMONE EXCRETION

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ABSTRACT

HMG-hCG therapy was performed on 109 patients who had previously received various forms of treatment but had failed to ovulate or become pregnant. From among the 109 patients, 80 (73.4%) succeeded in ovulation and 37 (33.9%) became pregnant. Ten patients with high FSH and low estrogen levels before the therapy failed to ovulate and were believed to have amenorrhea of ovarian origin. This indicated the importance of measurements of gonadotropin and estrogen prior to therapy with exclusion of patients in whom hMG-hCG therapy is expected not to be effective. Signs of ovarian hyperstimulation syndrome, such as ovarian enlargement, ascites and hydrothorax, were seen in 58% of 245 treated cycles. Our study revealed that there was remarkable increase in the levels of estrogen and progesterone in the majority of patients who presented clinical signs of ovarian hyperstimulation, indicating superovulation as the main cause of ovarian hyperstimulation syndrome which was confirmed at operation.

Key words: OVARIAN HYPERSTIMULATION; STEROID HORMONE; INDUCTION OF OVULATION; HMG

INTRODUCTION

Various methods with the purpose of induction of ovulation have been attempted in the treatment of anovulatory females in the past: however, the clinical results obtained from these treatments in severe forms of anovulation have been far from being satisfactory.

Since the report of Lunenfeld et al.¹⁾ in 1962, the use of human menopausal gonadotropin (hMG) in infertile women has been widely accepted. The efficacy of hMG-hCG therapy in induction of ovulation followed by pregnancy has been confirmed by Rosenberg et al.²⁾, Diczfalusy et al.³⁾ and others⁴⁾⁵⁾.

A thorough grasp of hormone dynamics of the individual patients is of extreme importance if one were to improve the effectiveness of hMG-hCG therapy and to prevent the occurrence of ovarian hyperstimulation syndrome.

This study was started with the purpose of investigating the correlation between the occurrence of ovarian hyperstimulation syndrome and hormone excretion pattern.

MATERIALS AND METHODS

Subjects for this study included patients with infertility due to anovulation. HMG-hCG therapy was performed in a total of 245 cycles for induction of ovulation. Prior to the

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therapy, the majority of these patients had received various forms of treatment but had failed to ovulate or become pregnant. These therapeutic maneuvers included thyroid, cyclic therapy and clomid.

Humegon, a product of Organon Ltd., which is a highly purified gonadotropin extracted from the urine of postmenopausal women (55-75 years old) was used. A 150 IU daily dose of hMG was administered until evidences of follicular maturation were detected. HCG was then administered in a dose of 3000 IU over a period of 3 to 5 days. To determine the time of ovulation, various criteria such as (1) the basal body temperature, (2) excretion of urinary pregnanediol and plasma progesterone, (3) endometrial histology were taken into consideration.

Urinary FSH and LH, urinary total estrogen and pregnanediol and plasma progesterone determinations were made prior to, during and after hMG-hCG therapy. Urinary FSH and LH and plasma progesterone assays were done by radioimmunoassay; total urinary estrogen by the simple and rapid method of Brown⁶, and urinary pregnanediol by gas liquid chromatography.

RESULTS

1. The Incidence of Induced Ovulations and Pregnancies

As shown in Table 1, hMG was administered to 109 patients in 245 cycles primarily for induction of ovulation. Ovulation was induced in 80 patients (73.4%) and in 182 cycles (74.3%). A total of 39 cycles of treatments were given to 20 patients with anovulatory cycles. Ovulation occurred in 19 cases (95.0%) and in 36 cycles (94.7%) and 7 cases (35.0%) became pregnant. Thirty-seven patients with grade 1 amenorrhea received a total of 85 cycles of treatments. Ovulation occurred in 66 cycles (77.6%) and 11 cases became pregnant. Forty-five patients with grade 2 amenorrhea received 107 cycles of treatments. Ovulation was induced in 75 cycles (70.1%) and 18 cases (40.0%) became pregnant.

2. HMG Treatment and Hormone Excretion

The determination of hormone excretion offers a valuable guide for the evaluation of the response and sensitivity of the ovaries and the effectiveness of gonadotropin therapy. Therefore, excretion patterns of various hormones were assayed and the results during hMG-hCG therapy were evaluated.

Table 1. Results of hMG-hCG Therapy in Anovulatory Patients

	No of Cases	Ovulated Cases (%)	No of Cycles	Ovulated Cycles (%)	Pregnant Cases (%)
Anovulatory Cycle	20	19 (95.0)	38	36 (94.7)	7 (35.0)
Secondary Aemnorrhea 1st Grade	37	32 (86.5)	85	66 (77.6)	11 (29.7)
Secondary Amenorrhea 2nd Grade	45	27 (60.0)	107	75 (70.1)	18 (40.0)
Primary Amenorrhea	7	2 (28.6)	15	5 (33.3)	1 (14.3)
Total	109	80 (73.4)	245	182 (74.3)	37 (33.9)

a) *The Gonadotropin Level and the Effectiveness of Ovulation Induction*

The correlation between FSH excretion prior to hMG-hCG therapy and the effectiveness of ovulation induction was investigated. As shown in Figure 1, ovulation could not be induced in all ten patients whose urinary FSH level was over 30 IU/day.

b) *The Urinary Estrogen Levels and the Effectiveness of Ovulation Induction*

Serial assays of urinary estrogen were performed during hMG-hCG therapy. As shown in Figure 2, urinary estrogen did not increase, maintaining a very low level, in patients who failed to respond to hMG.

An analysis of the relationship between urinary FSH and estrogen level and the effectiveness of ovulation induction revealed that ovulation was not induced in patients with high FSH and low estrogen levels, whereas ovulation was induced rather easily in those patients with relatively normal FSH and estrogen levels (Figure 1).

In patients with amenorrhea of ovarian origin with a hypergonadotropic hypogonadism pattern, it is difficult to induce ovulation even with hMG-hCG therapy.

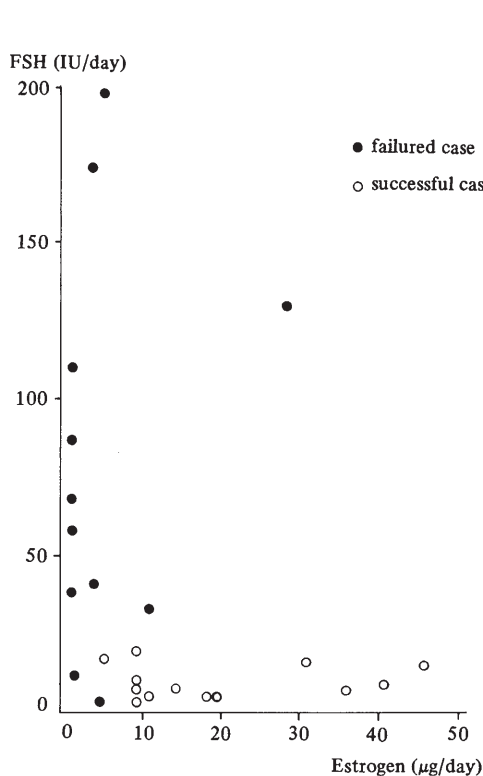


Fig. 1 Relationship between Urinary FSH and Estrogen and Effectiveness of Ovulation Induction prior to hMG-hCG Therapy

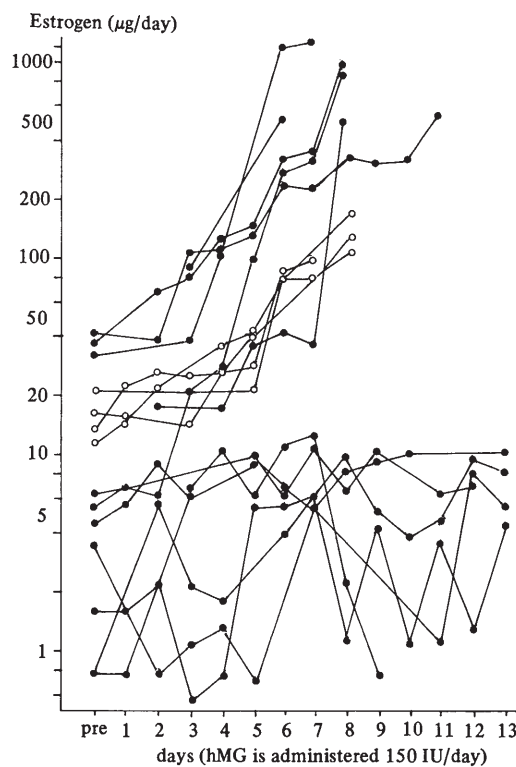


Fig. 2. Daily Determinations of Estrogen Excretion during hMG-hCG Therapy
 # ■ = cases who succeeded in ovulation-complicated with ovarian hyperstimulation syndrome
 ○ = cases who succeeded in ovulation without ovarian hyperstimulation
 ● = cases who failed in ovulation

3. Incidence of Ovarian Hyperstimulation Syndrome

Ovarian hyperstimulation syndrome is rather frequently encountered during hMG-hCG therapy. From among the 109 patients who received 245 treated cycles, ovarian enlargement (over hensegg-size) was observed in 58 cycles (23.7%), abdominal distention and pain in 43 (17.5%), ascites in 16 (6.5%), nausea and vomiting in 9 (3.6%), hydrothorax in 3 (1.2%) and dyspnea in 3 (1.2%) (Table 2).

a) Ovarian Hyperstimulation Syndrome and Hormone Excretion Pattern

The purpose of hMG-hCG therapy is aimed at enhancing the rate of ovulation and subsequent pregnancies on the one hand and to prevent, as much as possible, the occurrence of ovarian hyperstimulation syndrome.

Serial assays of urinary estrogen were performed during the administration of hMG and its correlation with the incidence of ovarian hyperstimulation syndrome was investigated. In the majority of patients, as shown in Figure 2, who presented clinical symptoms of hyperstimulation such as enlargement of ovaries, ascites etc., an acute increase of urinary estrogen was observed around the 5th day of treatment. The average excretion of estrogen in these cases prior to hCG administration was 692 ug/day.

In those patients with no signs of hyperstimulation, the average estrogen excretion was 112 ug/day, somewhat higher than that of control subjects with normal ovulatory cycles (67.6 ± 31.4 ug/day). On the other hand, the average estrogen excretion in unresponsive cases was 8.2 ug/day.

The plasma progesterone levels after the administration of hCG was assayed. As shown in Figure 3, the plasma progesterone levels were extremely high in the group of patients who developed ovarian hyperstimulation syndrome as compared to the excretion levels in the group with no signs of hyperstimulation (10.4 ± 6.9 $\mu\text{g/ml}$).

b) Ovarian Hyperstimulation Syndrome and Superovulation

The incidence of ovarian hyperstimulation syndrome during hMG-hCG therapy is relatively high and judging from the excretion of steroid hormones the occurrence of superovulation could be suspected.

Table 2. Classification of Hyperstimulation in 245 Cycles

Clinical Findings	No of cycles	%
Palpable Cyst	56	22.9
Enlarged Cyst (over hensegg size)	58	23.7
Abdominal Distension	25	10.2
Abdominal Pain	18	7.3
Ascites	16	6.5
Nausea	6	2.4
Vomiting	3	1.2
Hydrothorax	3	1.2
Dyspnea	3	1.2
Diarrhea	1	0.4
No Findings	108	42.0

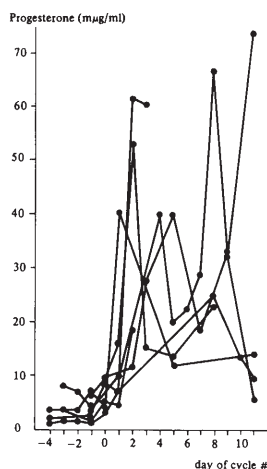


Fig. 3. Plasma Progesterone Levels of Ovulated Cases Induced by hMG-hCG Therapy Who Developed Ovarian Hyperstimulation Syndrome # "0" means the day of ovulation.

The steroid hormone levels were analysed in patients who were hospitalized to undergo partial resection of ovaries for treatment of ovarian hyperstimulation syndrome.

At operation of ovaries, the number of corpora lutea was counted in bilateral ovaries. As shown in Table 3, numerous corpora lutea were counted and multiple ovulations were confirmed. As with the steroid excretion pattern, the urinary estrogen prior to administration of hCG and the pregnanediol excretion after ovulation were far from the level in normal menstrual cycle.

Table 3. Operated Cases with Severe Ovarian Hyperstimulation Syndrome

Case	Age	Type of Anovulation	Dose of hMG (IU)	Dose of hCG (IU)	Total# Estrogen (ug)	## Pregnane-diol (mg)	Ovarian Enlargement (cm)	No of Corpora Lutea	Ascites
E.H.	27	Amenorrhea 2nd Grade	1950	12000	670	82.2	R: 7 × 9 L: 7 × 8.5	R: 9 L: 9	+++
M.S.	34	Anovulatory Cycle	1200	9000	172	116.0	R: 5 × 4 L: 5.5 × 5	R: 6 L: 9	+
T.M.	31	Amenorrhea 1st Grade	1200	24000	357	12.2	R: 6.5 × 5 L: 9 × 6	R: 5 L: 5	+
S.O.	28	Amenorrhea 1st Grade	1500	3000	464	19.0	R: 6.5 × 5.5 L: 6.5 × 5.5	R: 3 L: 2	++
N.I.	34	Amenorrhea 1st Grade	1500	9000	452	9.8	R: 8.5 × 6.5 L: 7 × 4.5	R: 2 L: 1	+

Estrogen the day before the injection of hCG
Pregnane-diol after ovulation

DISCUSSION

With the use of hMG in 109 patients with ovulatory failure, ovulation was induced in 80 patients and 37 patients became pregnant. In 45 cases of grade 2 amenorrhea who received 107 cycles of treatment, ovulation was induced in 27 patients.

Gemzell⁷⁾ reported that he succeeded in inducing ovulation in 90% of his cases treated with human pituitary gonadotropin. Rabau et al.⁸⁾ also reported a successful ovulation rate

of 75.4% with hMG preparation. Other reports give successful ovulation rate of about 70–90%⁹⁾¹⁰⁾.

These results were far superior to treatments used in the past, and could be further improved if steroid and gonadotropin determinations were performed prior to hMG-hCG therapy to exclude those cases with anovulation of ovarian origin.

On the other hand, various degree of ovarian hyperstimulation syndrome ranging from mild to severe form with ovarian enlargement, ascites and hydrothorax were observed.

Ovarian hyperstimulation syndrome was seldom encountered in unresponsive cases, but was observed in a rather high percentage of ovulated and pregnant cases.

Taymor¹¹⁾ reported that mild ovarian hyperstimulation was observed in 17% of the total cases, and in 45% of the patients with polycystic ovary. In our study mild to severe forms of ovarian enlargement were found in 46% of cases.

Serial determinations of daily estrogen excretion are of extreme importance in the evaluation of the sensitivity of ovaries and response to hMG-hCG therapy.

In order to clarify the cause and to inhibit severe results of ovarian hyperstimulation syndrome, wedge resection of enlarged ovaries was performed in patients with ovarian hyperstimulation syndrome. Development of multiple follicles and corpora lutea is thought to be the result of maturation of multiple follicles and superovulation in response to hCG administration, which result in secretion of large amount of estrogen and progesterone.

Our study indicated that the remarkable increase of estrogen and progesterone was observed in the majority of patients who presented clinical symptoms of hyperstimulation such as ovarian enlargement with ascites.

Spadoni¹²⁾ and Taymor reported that in patients with hyperstimulation, the estrogen level was extremely high prior to and after hCG administration. Kobayashi *et al.*¹³⁾ also reported abnormally high urinary pregnanediol after ovulation in patients with hyperstimulation, the high pregnanediol was probably due to supervolution.

A hypergonadotropic hypogonadism pattern of hormones was seen in the majority of patients who did not respond even to relatively large doses of hMG. Increase of urinary estrogen was not observed in these patients who were believed to belong to the category of primary ovarian failure.

Zarate¹⁴⁾ reported that urinary FSH level was high in those patients who failed to ovulate under hMG-hCG therapy. Baramki¹⁵⁾ and Koninckx and Brosens¹⁶⁾ described the same opinion. In other words, hMG-hCG therapy is inappropriate for patients whose pre-treatment urinary FSH value is high, representing a hypergonadotropic type, and they should be excluded from hMG-hCG therapy.

On the other hand, it may be possible to induce ovulation in patients with primary amenorrhea of a hypogonadotropic hypogonadism pattern if the method of administration and dosage are planned.

A proper grasp of the endocrinological status of each patients may enable us to obtain the ultimate objective of hMG-hCG therapy.

REFERENCE

- 1) Lunenfeld, B., Suluimovics, S., Rabau E., *et al.*: L'induction del l'ovulation dans les amenorrhea hypophysaires par un traitement combine de gonadotropines urinaires menopausiques et de gonadotropines chorioniques. *Compt. Rend. Soc. France Gynecol.*, 35, 346–351, 1962.

- 2) Rosemberg, E., Coleman, J., Demany, M., *et al.*: Clinical effect of human urinary postmenopausal gonadotropins. *J. Clin. Endocr. Metab.*, **23**, 181–190, 1963.
- 3) Diczfalusy, E., Johannisson, E., Tillinger, K.G., *et al.*: Comparison of the clinical and steroid metabolic effect of human pituitary and urinary gonadotropins in amenorrhoeic women. *Acta Endocrinol. (Suppl) (Kbh)*, **90**, 35–56, 1964.
- 4) Spadoni, L.R., Cox, D.W. and Smith, D.C.: Use of human menopausal gonadotropin for the induction of ovulation. *Am. J. Obstet. Gynecol.*, **120**, 988–993, 1974.
- 5) Oelsner, G., Serr, D.M., Mashiach, S., *et al.*: The study of induction of ovulation with menotropins: analysis of results of 1897 treatment cycles. *Fertil Steril.*, **30**, 538–544, 1978.
- 6) Brown, J.B., MacLeod, S.C., MacNaughtan, C., *et al.*: A rapid method for estimating oestrogens in urine using a semi-automatic extractor. *J. Endocr.*, **42**, 5–15, 1968.
- 7) Gemzell, C.: Treatment of female and male sterility with human gonadotropins. *Acta Obstet. Gynecol. Scand. (Suppl)*, **48**, 1–10, 1967.
- 8) Rabau, E., David, A., Serr, D.M., *et al.*: Human menopausal gonadotropins for anovulation and sterility. *Am. J. Obstet. Gynecol.*, **98**, 92–98, 1967.
- 9) Thompson, C.R. and Hansen, L.M.: Pergonal (menotropins): A summary of clinical experience in the induction of ovulation and pregnancy. *Fertil Steril.*, **21**, 844–853, 1970.
- 10) Ellis, J.D. and Williamson, J.G.: Factors influencing the pregnancy and complication rates with human menopausal gonadotropin therapy. *Br. J. Obstet. Gynaecol.*, **82**, 52–57, 1975.
- 11) Taymor, M.L. and Sturgis, A.H.: Induction of ovulation with human postmenopausal gonadotropin. *Fertil Steril.*, **18**, 181–190, 1967.
- 12) Spadoni, L.R., Kitchin, J.D., Schindler, A.E., *et al.*: Evaluation of ovarian response to HMG stimulation. *J. Clin. Endocr.*, **27**, 1738–1745, 1967.
- 13) Kobayashi, T., Kobayashi, T., Furuhashi, T., *et al.*: Induction of ovulation with HMG. *Obstet. Gynecol.*, **35**, 137–145, 1968. (in Japanese)
- 14) Zarate, A., Karchmer, S., Gomez, E., *et al.*: Premature menopause. *Am. J. Obstet. Gynecol.*, **106**, 110–114, 1970.
- 15) Baramki, T.A. and Jones, H.W.: Early premature menopause. *Am. J. Obstet. Gynecol.*, **96**, 990–993, 1966.
- 16) Knoinckx, P.R. and Brosens, I.A.: The “gonadotropin-resistant ovary” syndrome as a cause of secondary amenorrhea and infertility. *Fertil Steril.*, **28**, 926–931, 1977.