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Response to Repetitive Cycles of Ovulation Induction in the Same Women

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It has been theorized that the administration of human menopausal gonadotropin (hMG) in consecutive menstrual cycles will result in a poor follicular response in the second cycle. To examine this, 50 women undergoing ovulation induction in two consecutive cycles were assessed, using in each the same induction regimen during the initial 5 days. The remainder of each cycle was individualized according to their response. Nine women were anovulatory, 19 were oligoovulatory, and 22 ovulated regularly in unstimulated cycles. In repeat cycles only 3 of 50 had poor follicular development and did not receive human chorionic gonadotropin (hCG); all were anovulatory. Forty-two of 50 of the first cycles had continually rising estradiol (E_2), while 43 of 47 of the second cycles had rising E_2 patterns. Grouping the peak E_2 prior to hCG in the ranges <300, 300–699, 700–1099, and ≥1100 pg/ml, peaks in the second cycle were similar in 25 of 50, lower in 16, and higher in 9. Only 3 of 9 anovulatory women had similar peaks, as compared to 22 of 41 of the oligoovulatory and regularly ovulating women. Comparing the second to the first cycle, the day of hCG was within 1 day in 28 of 50 women, 2 or more days less than the first cycle in 6, and 2 or more days greater than the first cycle in 11. We conclude that in a successive cycle of ovulation induction (i) the follicular response is impaired in anovulatory women, but (ii) in oligoovulatory or regularly ovulating women, clinically significant differences in the estradiol response do not occur.

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INTRODUCTION

Prior to the introduction of in vitro fertilization (IVF), the use of human menopausal gonadotropins (hMG) was primarily for ovulation induction in women with conditions including hypothalamic amenorrhea, pituitary dysfunction, polycystic ovarian disease, and hyperprolactinemia (1). As such, the menstrual history of women receiving these medications could usually be characterized as amenorrheic/oligomenorrheic. Among these women, it has been suggested that response to a second immediately consecutive cycle of ovulation induction with hMG results in impaired follicular development.

With the advent of in vitro fertilization and gamete intrafallopian transfer (GIFT) programs, hMG is now routinely administered to regularly ovulating women (2–4), as well as amenorrheic women. Furthermore, some of these women may undergo repetitive cycles of stimulation because of poor stimulation or ovulation prior to oocyte recovery. However, the manner in which these women will respond to rapid repetitive cycles of ovulation induction is also unclear.

This report examines two issues. First, whether the follicular-phase response to a second consecutive cycle of ovulation induction is impaired; and second, whether the efficacy of the second cycle varies with the prior menstrual pattern (regularly menstruating, oligomenorrheic, or amenorrheic).

MATERIALS AND METHODS

A prospective study of ovulation induction in two consecutive menstrual cycles was undertaken at Yale University and Vanderbilt University. Included were women who had the same agents employed for ovulation induction in the initial part of the cycle. After the initial 5 days of stimulation, management was individualized in each cycle depending on the patient's response. Human chorionic gonadotropin (hCG), 10,000 IU, was administered im 24 hr after the last dose of hMG. Monitoring of the stimulation regimen was performed by serum estradiol (E_2) levels and by ultrasound examination of follicular development in women with high E_2 levels or those participating in an in vitro fertilization program. hCG was withheld if inadequate follicular development occurred as evidenced by the lack of a rise in serum estradiol levels. hCG was also withheld in those women with estradiol levels over 2000 pg/ml and those who had more than four follicles greater than 1.5 cm in diameter on ultrasound to avoid hyperstimulation. The specific timing of hCG administration was also individualized, but the general principle was to administer hCG at an E_2 level of approximately 700–1000 pg/ml or at an apparent plateau.

The protocols consisted of the administration of human menopausal gonadotropins, either 2 or 3 ampoules/day beginning on cycle day 3. In three women, clomiphene citrate, 100 mg/day, was also administered on days 3 through 7 of the cycle. In all patients, the same initial regimen was used in each cycle of each individual woman. The second cycle was initiated with the onset of menses after the first cycle.

Patients were characterized as having amenorrhea, oligomenorrhea, or regular menses in unstimulated cycles, based on menstrual history, basal body temperature charts, serum progesterone levels, and endometrial biopsies. Follicular response to hMG stimulation was assessed by the pattern of estradiol rise, the peak estradiol level, the number of ampoules of hMG utilized, and whether it was appropriate to administer hCG. With regard to the latter, it was inappropriate to administer hCG in those women having an inadequate E_2 rise. Women who developed high estradiol levels and whose hCG had been withheld because of concern for hyperstimulation were not considered to have had an inappropriate E_2 rise. The pattern of the estradiol rise was classified as continually rising until hCG was administered or could have been administered, as compared to those cycles in which there was a fall in E_2 prior to the time that hCG was or could have been administered. The number of ampoules of Pergonal utilized was the sum of the number of ampoules in each cycle. The peak E_2 levels were grouped into one of four ranges: <300, 301–700, 701–1099, and ≥1100 pg/ml.

Comparison of the follicular-phase response in the first cycle of ovulation induction and the second, immediately successive cycle of ovulation induction was performed using the paired *t* test, the chi-square test, or Fisher's exact test. Comparisons among the amenorrheic, oligomenorrheic, and regularly menstruating women were performed by Fisher's exact test. Significant was defined as $P < 0.05$. All data are expressed as mean ± SE.

RESULTS

A total of 50 women was identified who underwent ovulation induction utilizing the same stimulation protocol in two successive cycles. Of these, 22 ovulated regularly, 19 were oligoovulatory, and 9 were anovulatory.

In the initial cycle of ovulation induction, all of the patients had follicular stimulated development sufficient to receive hCG. In the successive cycle, 3 of 50 (6%) failed to do so; all were anovulatory in unstimulated cycles ($P = 0.004$ vs oligoovulatory and regularly ovulating women combined). Assessing the follicular phase by the E_2 pattern, 42 of 50 (84%) of the initial cycles had continually rising E_2. Such a pattern was manifested in 43 of 47 (91%) of the successive cycles (excluding the 3 which did not stimulate adequately).

As shown in Table I, the peak E_2 levels in the first and second cycles were similar in 25 of 50, lower in the second cycle in 16, and higher in the second

Table I. Peak Serum Estradiol (E_2) Levels (pg/ml) in Initial and Successive Cycles of Stimulation

Initial cycle	Successive cycle			
	<300	300–699	700–1099	>1100
<300	1	2		
300–699	2	6	3	
700–1099	1	3	11	4
>1100		2	8	7

cycle in 9. Only 3 of 9 (33%) anovulatory women had similar peaks in the two cycles, as compared to 22 of 41 (55%) of the oligoovulatory and regularly ovulating women. The day of hCG administration and ampoules of hMG administered in the two cycles are compared in Tables II and III, respectively. For the latter two parameters, no differences were observed among anovulatory, oligoovulatory, and regularly ovulating women.

DISCUSSION

Traditionally, human menopausal gonadotropins have been utilized primarily for ovulation induction in amenorrheic women; a vast literature has accumulated describing those experiences (1). Currently, hMG is in widespread use for recruitment of multiple follicular development for IVF and GIFT procedures, and at our centers is also used as empiric therapy in infertile women. However, it is unclear whether the principles of hMG therapy previously categorized and applied are also appropriate for management of its administration in regularly ovulating women.

In stimulated and unstimulated cycles, numerous factors have been identified which participate in the selection process. The steroid hormones estradiol, progesterone, and testosterone; follicular fluid proteins including oocyte maturation-inhibiting factor, inhibin, and oocyte maturation-stimulating factor; and granulosa-cell follicle-stimulating hormone (FSH) receptor concentration are among the factors involved in the selection process (5–11). The cumulative effect of these and other factors is that in unstimulated cycles, only one follicle continues to develop. However, it is possible to override these normal regulating factors by the administration of agents to stimulate multiple follicular recruitment. It is presumed that such multiple development represents rescuing follicles that would normally have become atretic. However, an alternate possibility is that follicles from upcoming cohorts may be recruited, such that future cohorts would become depleted of follicles (or at least leading follicles) so that immediate future cycles would be impaired.

Table II. Timing of hCG Administration in the Second Cycle of Ovulation Induction

	No. of women
2 or more days less than initial cycle	6
Within 1 day of initial cycle	28
2 or more days greater than initial cycle	11
Not given in second cycle[a]	5

[a] Three women had poor stimulation; two were at high risk for ovarian hyperstimulation syndrome.

Table III. Ampoules of hMG Administered in Successive Cycles

	No. of women
3 or more less in the second cycle	11
Within 2 of initial cycle	15
3 or more greater in the second cycle	24

Because of previous reports suggesting that women receiving the same agent(s) for follicular recruitment respond similarly in different cycles (12–15) and that changing the stimulation protocol will alter the response (13,14), this study required that the initial day of stimulation and the medication administered during the initial 5 days of stimulation be the same.

An effect of stimulation of multiple follicular recruitment on the outcome of a second successive cycle would not be unexpected. In the report on unstimulated cycles in the rhesus monkey, diZerega and Hodgen (10) demonstrated an effect of progesterone secretion by the corpus luteum of the preceding cycle on the subsequent ovarian response, such that the ovary containing the dominant follicles tended to alternate. diZerega *et al.* (6) have also described modulation of the follicular response to gonadotropin stimulation and have identified this effect of be, at least in part, the result of an ovarian peptide. This thus strongly suggests a direct modulation of ovarian follicular selection by intraovarian events and/or ovarian secretions.

Thus it is not surprising that stimulation in two successive cycles with hMG in anovulatory women could result in impairment in the second cycle. Three of nine anovulatory women (33%) had poor successive cycles. The explanation for this impairment is unknown but could represent relative ovarian unresponsiveness due to the altered hormonal milieu as described above or depletion of the cohort of follicles attempting to be stimulated in the second cycle. This observation is in part consistent with that of Crooke *et al.* (19), who compared consecutive cycles of hMG administration in six women and observed that a 56% increase in hMG

administration was required to increase estrogen excretion 35 μg/24 hr above baseline in the second cycle. However, this increase reflected changing requirements in three of six women (50%). When combined with six additional women who received a gonadotropin preparation with an FSH:LH (luteinizing hormone) ratio of 5.1:1.0, 5 of 12 women (42%) required increased gonadotropin administration (4 of 10, or 40%, among women with anovulation), rates similar to those described in this report.

In contrast, in the regularly ovulating and oligoovulatory women in this report, there was no apparent impairment in follicular-phase response in the second successive cycle of multiple follicular recruitment. It is unlikely that this observation represents a direct hypothalamic–pituitary effect because these are not the sites of action of hMG in ovulation induction. However, an indirect hypothalamic–pituitary effect could not be entirely excluded. Thus it is most likely that this phenomenon represents an interovarian or intraovarian effect.

These observations have implications for regularly ovulating and oligoovulating women in IVF and GIFT programs. With a pregnancy rate of 10% in such women given hMG empirically while awaiting their turn for IVF (20), this report suggests that such treatment will not impair the follicular-phase response in regularly ovulating or oligoovulating women in their IVF-ET cycle. Whether this observation can be extended to include women undergoing multiple consecutive cycles of recruitment of multiple follicular development is currently unclear. Nevertheless, it would appear reasonable to attempt empiric therapy in women with patent fallopian tubes to assess their response to that particular stimulation protocol. Subsequently, if the initial response was acceptable, the same protocol could be utilized for IVF-ET or GIFT. Alternatively, if the initial response was unacceptable, the stimulation protocol in subsequent cycles could be altered.

In conclusion, this report demonstrates, albeit with a small number of patients, that the performance of ovulation induction by gonadotropin administration in two successive cycles will result in an impaired follicular-phase response in the second cycle in anovulatory women. However, in regularly ovulating or oligoovulating women, gonadotropin administration in sequential cycles does not impair the follicular phase response in the successive cycle.

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