

Premature luteinization: treatment and incidence in natural cycles

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The incidence of premature luteinization was evaluated in 400 women with a history of infertility (≥ 18 months). After its diagnosis, this condition was treated with ovulation-inducing drugs in the early follicular phase in an attempt to accelerate follicular maturation before the luteinizing hormone (LH) surge. Premature luteinization was diagnosed if serum progesterone levels > 1.5 ng/ml were associated with an LH surge before the serum oestradiol level reached 200 pg/ml and before the follicle was mature. Fifty-two of 400 (13%) women demonstrated premature luteinization in two consecutive cycles. Fourteen of 52 (27%) women corrected the problem with a clomiphene citrate regimen, as compared with 32 of 38 (75%) treated with HMG and HCG; conception rates were 83 and 50%, respectively, for the patients who responded to the two regimens. Overall, regimens utilized in this study resulted in a 58% pregnancy rate in 6 months.

Key words: natural cycles/premature luteinization/progesterone

Introduction

Premature luteinization, in which luteinizing hormone (LH) surges result in a rise in progesterone (P) before follicular maturation is achieved, is a recognized problem in women who have been treated with human menopausal gonadotrophins (HMG) to induce multiple follicular growth (Fleming and Coutts, 1986). Moreover, premature luteinization has been appreciated as a cause of pregnancy failure in anovulatory women who were given HMG in an attempt to stimulate single follicular maturation (Zimmerman *et al.*, 1984; Fleming *et al.*, 1985).

We examined the incidence of premature luteinization (two consecutive cycles) in infertile women who had not received ovulation-inducing drugs. In addition, we evaluated several treatment regimens in the patients found to have premature luteinization.

Finally, we compared the incidence of premature luteinization

in women who conceived within 6 months with those who failed to conceive, in addition, determining the incidence of premature luteinization in conception cycles.

Materials and methods

Diagnosis of premature luteinization

We evaluated 400 women not receiving ovulation-inducing drugs during a 6-month time period, each of whom had a history of at least 18 months of infertility. The mean duration of infertility was 4.1 years ranging from 1.5 to 13 years. Two hundred and forty-eight women had primary infertility whereas 152 had secondary infertility and their average age was 33.4 years (range 24-45 years). Pelvic sonography and measurements of serum oestradiol (E_2), progesterone (P) and LH levels were used to evaluate follicular maturation. Serum oestradiol assays were performed using a solid phase radioimmunoassay (Diagnostic Products, Los Angeles, CA), P by a competitive binding radioimmunoassay (Amersham Corporation, Arlington Heights, IL) and LH using a double antibody radioimmunoassay (Amersham Corporation, Arlington Heights, IL). These evaluations were performed daily beginning 16 days before the expected menses and continuing until serum P levels were > 2 ng/ml.

Premature luteinization was diagnosed if a serum P level > 1.5 ng/ml was associated with an LH surge occurring before the serum E_2 level reached 200 pg/ml and before the follicle was considered mature (minimum of 18 mm average diameter) as determined by pelvic sonography (Hackeloer, 1978; Check *et al.*, 1984). The LH surge was defined as a doubling of the level from the preceding day as long as the rise continued the next day; the peak LH surge generally attained at least a 5-fold rise. In fact, the rise in serum P prevented the serum E_2 level from reaching 200 pg/ml. If follicular growth was still demonstrated when the serum P level had reached 2.5 ng/ml, daily monitoring was discontinued.

All the patients in this study were evaluated during two consecutive cycles. Patients who demonstrated premature luteinization in two consecutive cycles were eligible to receive treatment.

Treatment for premature luteinization

A sequential treatment approach, with three possible treatment steps, was used.

Treatment A. After the diagnosis of premature luteinization had been established in two consecutive cycles, the patients were treated with clomiphene citrate, 50 mg, from day 3 to day 7 of

the cycle. If a mature follicle of 18 mm diameter by ultrasound associated with a serum E_2 of 200 pg/ml was achieved, a dose of 10 000 units of human chorionic gonadotrophin (HCG) was given. The treatment was monitored by ultrasound, which was repeated 2 or 3 days after HCG administration. Release of the ovum was confirmed by a reduction of at least 5 mm in the follicle size 2–3 days after maturity was established, and usually confirmed by the presence of fluid in the pelvic cavity.

Treatment B. Failure to correct the premature luteinization or to release an egg after two cycles of treatment A prompted the use of this next treatment step in the subsequent cycle. Treatment started with HMG on cycle day 3 followed by 10 000 units of HCG when the leading follicle was mature. The HMG was usually started at a daily dose of 150 IU for at least 3 days and then further modifications were made based on the serum E_2 , P, LH and pelvic sonography.

Treatment C. If the HMG treatment was not successful in correcting the premature luteinization after two cycles, the patients were given ethinyl oestradiol (EE), 50 μ g, from day 3 of the cycle. Treatment with HMG began on day 6 of the same cycle and the HCG was administered as a single dose of 10 000 units. The EE was continued until HCG was given.

Other treatment

Other factors potentially related to the patients' infertility (e.g. male and cervical factors) were evaluated and treated concurrently with the premature luteinization.

It should be noted that only 35% of the patients had previous tubal studies, either hysterosalpingogram or laparoscopy; in no instance was bilateral tubal occlusion present. No additional tubal studies were performed during this study. All patients were given the option of having tubal studies but 65% elected to defer them since another remediable cause of infertility was found.

Outcome of treatment and analyses

A chi-square analysis was used to determine the likelihood that chance alone would be responsible for premature luteinization occurring in two consecutive cycles. A P value of <0.05 was considered statistically significant.

The treatment that successfully corrected the premature luteinization and resulted in release of the ovum was continued for at least 6 months or until a pregnancy occurred. The number of pregnancies occurring in the 6-month period beginning with the first cycle in which ovulation was corrected were recorded. The number of pregnancies in the study population, i.e. women diagnosed with premature luteinization, was compared with the expected value for a population of normal women during a 6-month period using a life table analysis.

Comparison of premature luteinization in conceiver versus non-conceivers

Those women who did not demonstrate premature luteinization in the first two consecutive cycles were monitored in many of their subsequent cycles to compare the incidence of this condition in conceiver versus non-conceivers and to determine its incidence in conception cycles.

Results

Of the 400 women, 56 (14%) demonstrated premature luteinization during the first cycle and all but four of these 56 (13%) also fulfilled the diagnostic criteria during their next cycle. The mean serum levels of E_2 , P and LH and the mean follicular diameter in the women diagnosed with premature luteinization are presented in Figure 1.

It is interesting to note that only six of the 331 women (1.8%) who did not demonstrate premature luteinization during the first cycle did so during the second cycle. Thus, when the incidences of second-cycle premature luteinization are compared in patients who demonstrated this problem in the first cycle and those who did not, the likelihood of premature luteinization being a persistent infertility factor, rather than a chance event, was found to be high ($P = 0.0001$).

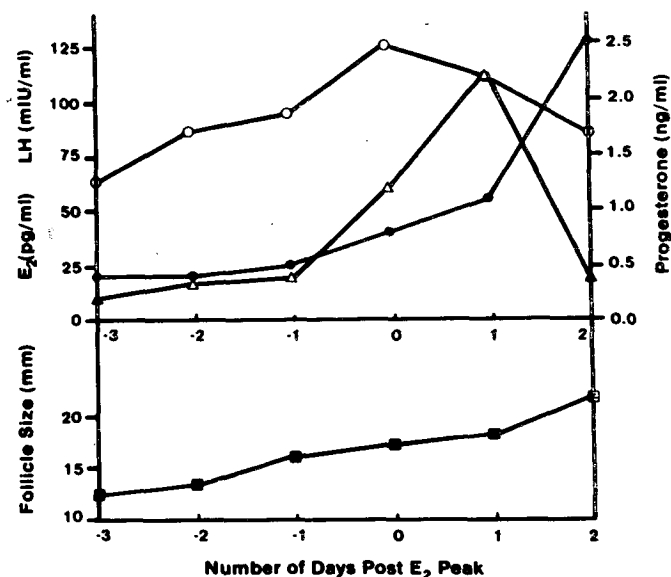


Fig. 1. Mean oestradiol, progesterone, LH assays correlated with follicle size in patients with premature luteinization. Note that the follicles continue to enlarge even after the E_2 peak and by 2 days post E_2 peak most attained an appropriate diameter for a mature follicle. Thus ultrasound alone without hormonal studies is insufficient in determining follicular maturity. The highest serum E_2 attained was 125 pg/ml. ■—■, follicle size; ○—○, serum [E_2]; △—△, serum [LH]; ●—●, serum [progesterone].

Table I. Response of patients with premature luteinization to three different treatment protocols

Treatment	No. cases treated	No. cases corrected	No. pregnant corrected
Clomiphene + HCG	52	14 (27%)	10 (20%)
HMG + HCG	38	32 (84%)	20 (53%)
Ethinyl oestradiol + HMG-HCG	6	6 (100%)	0

The three treatments were given sequentially. All patients were offered clomiphene and HCG first. Only those failing to correct premature luteinization after two treatment cycles were offered the next therapy. Once a treatment regimen corrected the problem the patients were treated for six cycles (unless pregnancy intervened) and the 6-month period pregnancy rate was calculated.

The results of the various treatment regimens, in terms of correction of premature luteinization and achievement of pregnancy, are shown in Table I. The regimens that utilized clomiphene citrate and HCG corrected premature luteinization in 14 of 52 cases (27%) and resulted in the achievement of 10 (20%) pregnancies. The four patients failing to conceive were given 22 cycles of treatment and premature luteinization was corrected in 17 (77%).

In contrast, regimens consisting of HMG and HCG corrected the problem in 32 of 38 (84.2%) cases, with 20 (52.6%) of the women achieving pregnancy. The 12 women not conceiving were given 64 cycles of treatment and premature luteinization was corrected in 58 (90%). Four of these pregnancies were spontaneously aborted; however, two of the patients who aborted achieved pregnancies within two cycles after they had resumed the treatment and one of these patients had a viable triplet gestation. Thus, four viable neonates were subsequently born.

All eight patients treated with EE, HMG and HCG corrected the previous luteinization problem and released ova; however, none of these women achieved a pregnancy. These eight women were given 43 cycles of therapy and premature luteinization was corrected in 32 cycles (74%).

These results show that 22 of the 52 patients (42%) failed to conceive after 6 months of treatment for correction of premature luteinization. However, if the 52 patients are divided into two groups—those for whom all other infertility factors were corrected versus those with inadequate correction of other factors—24 of 34 (71%) in the former group and six of 18 (33%) in the latter group conceived during the 6-month period. Even in the 'corrected' group, tubal factors had not been evaluated in a significant minority (eight of 34 = 23.5%). A life table analysis comparing the incidence of pregnancies in these two groups with that expected for a normal population is shown in Figure 2.

A total of 348 women not demonstrating premature luteinization in the first two cycles had follicular maturation studies in 1320 subsequent cycles during a 6-month period. Pregnancies occurred in 249 patients (71.5%). Follicular maturation studies were available in 161 conception cycles; premature luteinization did not occur in any cycle. A total of 772 cycles in those achieving

pregnancies were also evaluated as were 407 cycles in non-conceivers. The incidence of premature luteinization in the former was 2.2% (17/722) and 3.7% (15/407) in the latter.

Discussion

The results of this study indicate that premature luteinization can be an important infertility factor in a subset of infertile women. The regimens utilized in this study to treat premature luteinization resulted in an overall pregnancy rate of 58%. Although this conception rate is somewhat lower than that expected for normal women, the cumulative probability of pregnancy in the subset of women in whom other infertility factors and premature luteinization were corrected compares quite favourably with that of the normal population.

The importance of attaining a follicle capable of increasing the serum E_2 level to 200 pg/ml was demonstrated by the high conception rate achieved with P supplementation, administered in the luteal phase, in women with luteal phase defects (Check *et al.*, 1988). This can be contrasted with the poor success of similar therapy in women with luteal phase defects whose serum E_2 levels remained <200 pg/ml (Check *et al.*, 1988). The conception rate of the latter group improved when they were treated with ovulation-inducing drugs plus P. The difference between the patients with premature luteinization and those with immature follicles is that in the former group, the P level rises before the E_2 level reaches 200 pg/ml and a mature follicle is still present, whereas in the latter group, the serum P level does not rise until follicular rupture has been demonstrated.

The objective of using ovulation-inducing drugs to treat premature luteinization was to accelerate follicular maturation, hypothesizing that the premature rise in P would occur at a fixed time interval from the recruitment of the follicle. Although only 14 of 52 patients (27%) corrected the problem with clomiphene citrate, 83% (10/14) of this corrected group conceived during the next 6 months. Six of the 10 received clomiphene citrate 50 mg days 3–7 and the other four were given 100 mg days 3–7; also five of them had been placed on supplemental EE (two with 20 μ g and three with 50 μ g) to improve the cervical mucus. In contrast, regimens containing HMG corrected the ovulation problem for the remaining 38 women, but only 20 (53%) of these women conceived. The reduced pregnancy rate in the HMG-treated patients was probably related to inadequate correction of other infertility factors in 17 of 38 of these women, whereas other infertility factors were fully corrected in 11 of 12 of the clomiphene-treated women. The resulting conception rate of 60% (14 of 23) for HMG-treated patients who had all other infertility factors corrected was still lower than the 83% rate for clomiphene-treated women.

The failure of conception in the patients treated with the oestrogen/HMG regimen may have been related to other, uncorrected infertility factors, which were present in seven of 10 of these patients. Alternatively, the oestrogen may have had a negative influence, perhaps by stimulating an abnormally thickened endometrium. Pregnancies have been observed with this regimen during treatment of cervical factor (Check *et al.*, 1986) or hypergonadotrophic hypogonadism (Check and Chase,

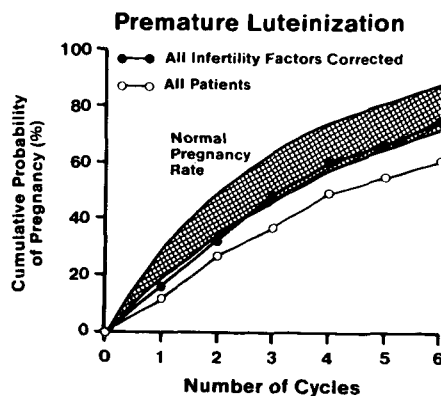


Fig. 2. Cumulative probability of pregnancy in patients with premature luteinization following therapy. The limits for the normal range were calculated on the basis of a normal pregnancy rate between 17 and 25% per month (see Goldfarb *et al.*, 1982).

1984). However, if utilization of high dose oestrogen therapy to inhibit premature gonadotrophin release continues to result in conception failure, treatment with leuprolide acetate followed by HMG might be attempted to suppress premature gonadotrophin release. This approach has been used in patients undergoing superovulation regimens in preparation for in-vitro fertilization and gamete intra-Fallopian transfer (Awadalla *et al.*, 1987) and in women with polycystic ovarian syndrome who are found to have premature luteinization when treated with ovulation-inducing drugs (Dodson *et al.*, 1987).

The data demonstrated that 93% of women found to have premature luteinization in the first cycle also exhibited this problem in the second. This compares with the very low incidences found in conceivers (2.2%) and non-conceivers (3.7%). The fact that no patient had premature luteinization in a conception cycle supports this condition as a reason for failure to conceive in a given cycle.

The data suggest that the use of HMG from the early follicular phase is an effective treatment of premature luteinization. A randomized study comparing HMG-HCG to leuprolide acetate suppression of gonadotrophins followed by HMG-HCG in alternating cycles is planned.

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