

New Approaches to the Diagnosis and Therapy of the Luteinized Unruptured Follicle Syndrome

Jerome H. Check, M.D.

Jeffrey S. Chase, M.D.

Harriet G. Adelson, B.S.

Carole Dietterich, R.T., R.D.M.S.

From the Department of Obstetrics and Gynecology,
Division of Reproductive Endocrinology
The Jefferson Medical College of Thomas Jefferson University
Philadelphia, Pennsylvania

ABSTRACT: Ultrasound has been employed in diagnosing the luteinized unruptured follicle syndrome (LUF). Eighty-nine of 333 infertility patients were found to have LUF. The patients were divided into three groups. Group 1 was on no fertility medication. Twenty-five of 39 of this group released with HCG alone. Ten of the nonreleasers to HCG did release with HMG mixed with HCG.

Group 2 patients had been treated with clomiphene and found to have LUF. Thirteen of 16 patients released with HCG and one of the failures released with HMG-HCG.

Group 3 patients had been treated with HMG and had failed to release the ova despite HCG. Thirty-one of 33 did release with HMG-HCG.

Twenty-six of 89 patients achieved a pregnancy within six months of therapy and 20 of 36 patients with all fertility factors corrected achieved a pregnancy.

INTRODUCTION

One of the subtle causes of infertility is the luteinized unruptured follicle (LUF) syndrome in which women appear to be ovulating by progesterone criteria and yet do not release the ovum. This syndrome has been diagnosed by the demonstration of the absence of an ovulation stigma during an appropriately timed laparoscopy,^{1,2} or by demonstration of reduced peritoneal volume and concentration of 17-beta estradiol and progesterone in LUF compared to ovulating women.³

There is some evidence that this syndrome may occur with increased frequency in women with ovulations induced by clomiphene citrate,⁴ endometriosis,⁵ or unexplained infertility.² However, if one is to determine whether any given therapy is correcting this abnormality some noninvasive monitoring techniques would be far more efficacious. Ultrasound is a benign

noninvasive technique and there is evidence that this modality may be used to diagnose the luteinized unruptured follicle syndrome.⁶

This study was designed to see the efficacy of various treatment regimes in correcting the LUF syndrome as detected by pelvic sonography.⁷⁻¹⁰

MATERIALS AND METHODS

Three hundred thirty-three patients being treated for infertility were evaluated for the luteinized unruptured follicle syndrome. The requirements for selection for the study included at least a two-year duration of infertility and at least eight previous unsuccessful treatment cycles unless there was no abnormality found. Two consecutive cycles were evaluated.

A patient was considered to have the LUF syndrome if she failed to release the ovum from the follicle in both baseline cycles evaluated. A follicle was consid-

ered to be mature if the size attained was between 18 and 24 mm.⁷⁻¹⁰ Evidence of follicle rupture included a rapid decrease in follicular size by 5 mm within 72 hours of reaching an 18-24 mm size and free fluid in the cul-de-sac.¹¹ We found free fluid to be an unreliable sign and relied on diagnosing the LUF by no decrease in follicular size 72 hours after reaching a mature size with regression of the cervical mucus. The patients were monitored on a daily basis by pelvic ultrasounds and cervical mucus evaluation beginning 16 days before their expected menses. All ultrasounds were performed by only two ultrasonographers on two identical-type machines and each patient was evaluated by only one ultrasonographer on only one machine. Other ancillary evidence for luteinization included endometrial thickening by ultrasound and an increase in serum progesterone levels over 3 ng/mL.

RESULTS

Three hundred and thirty-three patients were evaluated. Eighty-nine patients failed to release an ovum by ultrasound criteria in two consecutive cycles. Twenty patients released in only one of two cycles, whereas 224 patients released in both cycles.

The 89 patients consisted of 39 patients found to have the LUF syndrome and were not on any fertility medication at the time (Group 1), 17 patients who were being treated with clomiphene citrate (Group 2) and 33 patients who were being treated with HMG (Group 3).

The success with therapy with either (1) 10,000 units HCG (or 15,000 if failure of release occurred with the first dosage), or (2) a combination of 15,000 IU HCG and 150 IU HMG injections given at the same time, or (3) HMG therapy from the 5th day of cycle to formation of a mature follicle of 18-24 mm with 10,000 or 15,000 units HCG given to release the ovum, or (4) HMG therapy with the release injection of HMG-HCG, is seen in Table I. Twenty-five out of the 39 patients in Group 1 on no ovulation-inducing drugs released the ovum with HCG given when the follicle reached an 18-24 mm size. The 14 patients who did not release were given a release injection of HMG-HCG and 10 patients in this group released. Only one of the four remaining patients failed to release when they were treated with HMG from day 5 and given either HCG or HMG-HCG for release.

Forty-eight patients appeared to have perfect cycles on clomiphene citrate as evidenced by serum progesterone levels over 15 ng/mL one week after

TABLE I
Effectiveness of various treatment modalities on the release of the ovum in patients with the LUF syndrome.

	Group 1	Group 2	Group 3
Total # of patients:	39	16	33
10,000 or 15,000 units HCG	25	13	
HCG (15,000 units) and HMG (150 units)	10	1	31
HMG therapy day 5 to ovulation and release with HCG	1	1	
HMG therapy day 5 to ovulation and release with HMG-HCG	2	1	

Group 1=LUF patients not treated with ovulation inducing drugs

Group 2=LUF in patients Rx with clomiphene citrate

Group 3=LUF in patients Rx with HMG

The number to the right of each Rx indicates the number of patients releasing the ovum with that therapy in each of the 3 groups.

reaching a mature follicle and a two-week rise in their basal body temperature chart. However, 17 patients were diagnosed as having the LUF syndrome. Sixteen patients were first treated with HCG when a mature follicle was reached and 81% released. One of the three subsequently released the ovum with HMG-HCG while the other two patients required HMG therapy and released with either HCG or HMG-HCG.

In 33 HMG patients who did not release with conventional HCG therapy, 31 released with HMG-HCG. Both of the failures had endometriosis involving the ovaries and one did release following surgical therapy but still needed HMG-HCG.

The average duration of infertility in these LUF patients was 3.8 years with an average of 2.4 years of previously unsuccessful therapy. Twenty-six of 89 patients achieved a pregnancy within six months on this therapy. However, if one isolates the patients where all other factors relating to infertility were normal or corrected, then 20 of 36 patients achieved a pregnancy within six months of therapy (Table II). Fifty-three patients had been considered infertile secondary to various factors, eg extensive adhesions, endometriosis, or male factor that was inadequately corrected. Nevertheless, therapy directed to the LUF syndrome still enabled six patients to conceive.

TABLE II
Pregnancy rates in patients with exclusively LUF syndrome or LUF and other infertility factors corrected.

	Group 1	Group 2	Group 3
# Patients	18	8	10
# Pregnant	12	3	5

Group 1 = LUF patients not treated with ovulation inducing drugs
 Group 2 = LUF in patients Rx with clomiphene citrate
 Group 3 = LUF in patients Rx with HMG.

DISCUSSION

Recently, the incidence of the LUF syndrome in ovulating patients was found to be about 5%.¹² If this is a chance random event, the odds of this happening in two consecutive cycles would be 1 in 4000. Twenty-seven percent of patients with recalcitrant infertility problems were found to have the LUF syndrome based on failing to release the ovum by ultrasound in two consecutive cycles. These patients had an average infertility duration of 3.8 years and had seen an average of 2.1 previous infertility specialists. Thus the incidence of LUF might be significantly lower in less recalcitrant infertility cases.

Theoretically, one possible cause of failing to release the ovum is the inability to mount a proper LH surge. Since HCG has similar biological action as LH, a bolus injection of HCG was employed if the follicle achieved a size of 18-24 mm and the post-coital test was good. At the present time we employ HCG not only when the follicle is 18-24 mm and the post-coital test is good, but when the serum estradiol must be at least 200 pg/mL per follicle.

There is a surge not only of LH at mid-cycle before ovum release occurs but also an FSH surge. We hypothesized that since HCG has predominantly LH action, perhaps some patients need additional FSH also in order to release the ovum. Therefore, if HCG alone failed we mixed 15,000 units with 150 IU of HMG and employed this combination in the next cycle. Seventeen patients failing to release with HCG alone did release with HMG-HCG. Thirty-three HMG-treated patients failed to release the ova with HCG. Thirty-one released with HMG-HCG.

The efficacy of this therapy is suggested by the fact that 12 of 18 patients who had no other detectable

cause of infertility with an average infertility duration of 3.3 years achieved a pregnancy within six months of therapy exclusively directed to releasing the ovum. Although only six of 53 patients with other associated infertility factors became pregnant by correcting the LUF syndrome, nevertheless, since the diagnosis and therapy is relatively simple it is worth an attempt even in cases considered infertile secondary to adhesions, endometriosis, male factor, etc.

This study would have had more meaning if some patients were given a placebo instead of HCG or HMG-HCG in a randomized double-blind fashion. Perhaps emotional factors also contribute to releasing the ovum. Although limiting our study to those patients with long-term infertility problems, most of whom had had other treatment, helps make the investigation more believable, we still hope that someone can corroborate the data in a true, double-blind study. The nature of our private practice prevented us from using proper controls.

ACKNOWLEDGEMENT

We want to thank Amy Rankin, R.T., R.D.M.S. and Joanne Liss for their technical assistance.

REFERENCES

1. Marik J, Hulka JF: Luteinized unruptured follicle syndrome: a subtle cause of infertility. *Fertil Steril* 29:270, 1978.
2. Koninckx PR, Heyns WJ, Corvelyn PA et al: Delayed onset of luteinization as a cause of infertility. *Fertil Steril* 29:266, 1978.
3. Koninckx PR, DeMoor P, Brosens IA: Diagnosis of the luteinized unruptured follicle syndrome by steroid hormone assays on peritoneal fluid. *Br J Obstet Gynaecol* 87: 929, 1980.
4. Jewelewicz R: Management of infertility resulting from anovulation. *Am J Obstet Gynecol* 122:909, 1975.
5. Brosens IA, Koninckx PR, Corvelyn PA: A study of plasma progesterone, oestradiol-17B, prolactin and LH levels, and the luteal phase appearance of the ovaries in patients with endometriosis and infertility. *Br J Obstet Gynaecol* 85:246, 1978.
6. Coulam CB, Hill LM, Breckle R: Ultrasonic evidence for luteinization of unruptured preovulatory follicles. *Fertil Steril* 37:524, 1982.
7. Robertson RD, Picker RH, Wilson PC et al: The assessment of ovulation by ultrasound and plasma estradiol determinations. *Obstet Gynecol* 54:686, 1979.
8. Smith DH, Picker RH, Sinosich M: The assessment of ovulation by ultrasound and estradiol levels during spon-

- taneous and induced cycles. *Fertil Steril* 33:87, 1980.
9. Hill LM, Breckle R, Coulam CB: Assessment of human follicular development by ultrasound. *Mayo Clin Proc* 176, 1982.
 10. O'Herlihy C, de Crespigny LC, Lopata A et al: Preovulatory follicular size: a comparison of ultrasound and laparoscopic measurements. *Fertil Steril* 34:24, 1980.
 11. de Crespigny LC, O'Herlihy C, Robinson HP: Ultrasonic observation of the mechanism of human ovulation. *Am J Obstet Gynecol* 139:636, 1981.
 12. Kerin JF, Kirby C, Morris D et al: Incidence of the luteinized unruptured follicle phenomenon in cycling women. *Fertil Steril* 40:620, 1983.
 13. Kerin JF, Edmonds DK, Warnes GM et al: Morphological and functional relationships of graafian follicle growth to ovulation in women using ultrasonic, laparoscopic and biochemical measurements. *Br J Obstet Gynaecol* 88:81, 1981.