THE IMPACT OF LUTEINIZED UNRUPTURED FOLLICLE (LUF) ON OUTCOME OF CONTROLLED OVARIAN STIMULATION:

IS THERE A RELATION TO STIMULATION PROTOCOL ?

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ABSTRACT

Introduction : LUF is a form of anovulation and a subtle cause of female infertility. The syndrome cannot be diagnosed by traditional progesterone-dependent ovulation detection methods. Without the use of either transvaginal ultrasound (TVS) or laparoscopy as well as progesterone assay, LUF syndrome may go unnoticed.

Objective : To assess the prevalence of LUF and the effect of stimulation protocol on its development as diagnosed by serial TVS and midluteal progesterone (MLP).

Patients and Methods : A total of 300 cycles in 228 patients were monitored for various causes of infertility under different stimulation protocols: clomiphene citrare (CC)/HCG, or CC plus HMG/HCG, or HMG/HCG. Serial TVS was started from days -5 to days +5 (The day of HCG trigger of ovulation was cycle day zero). MLP was measured on day +7. TVS evidence of LUF was persistence of unruptured preovulatory follicle(s) up to day +5 together with bichemical evidence of luteinization (MLP ≥ 1 ng/mL. Luteal phase length was measured to identify short luteal phase defect. Normal ovulatory cycle was diagnosed by TVS evidence of follicular rupture (visible corpus luteum with or without free fluid in DP) and biochemical evidence of good luteal function (MLP ≥ 10ng/ml) Luteal phase defect (LPD) was diagnosed by MLP<10 & >1 ng/ml.

Results : Of the total 300 cycles in 228 patients, 16 cycles in 15 patients were diagnosed as LUF giving a prevalence of 9% of cycles. Mean MLP was significantly lower in LUF cycles compared to normal ovulatory cycles (9.1±5.9 vs 21.9±1212 ng/mL respectively) (P<0.001). CC/HCG protocol was used in 48% of LUF cycles compared to 18.6% of normal cycles (P<0.001), while CC plus HMG/HCG or HMG/HCG were used in (40%, 36.9% in LUF and, normal ovulatory cycles respectively) (P=0.07). The percentage of PCOD cases was not significantly different in both groups (40% & 31% in LUF & normal ovulatroy cycles respectively). Although CC stimulation was used in 154/228 first cycles (35%) and 49/70 repeat cycles (35%), only 2 cases had recurrent LUF in first and repeat cycles of same patients. Although mean luteal phase length was not significanlty different (14.3±2.5 days vs 15.7±2.5) days in LUF and normal cycles respectively), 60% of LUF cases had MLP < 10 ng/ml (compared to none of the normal control. Cycle pregnancy rate was 21% in the normal cycles and zero in LUF cycles.

Conclusions : LUF as a clinical entity is to be suspected in cases treated by controlled ovarian stimulation employing CC and HCG protocol. About two thirds of LUF cases are associated with luteal phase defect. Our Data showed that LUF in stimulated cycles is a transient cycle phenomena related to subtle cycle features rather than constant patient

feature and is not a persistent cause of female infertility. It also has an undermining effect on the outcome of treatment cycles in terms of midluteal phase progesterone level and pregnancy rate. Both LUF and luteal phase defect associated with CC/HCG stimulation partly explain the discrepancy between ovulation rate detected by hormone assay and pregnancy rate. Combined serial ultrasound monitoring and midluteal progesterone assay are essential for diagnosis of luteinized unruptured follicle.

Key words : Luteinized unruptured follicle-Controlled Ovarian Stimulation

INTRODUCTION

Luteinized unruptured follicle (LUF) syndrome is defined as failure of ovulation in which despite the absence of follicular rupture and release of the oocyte, the unruptured follicle undergoes luteinization under the action of L.H. In such cases normal production of progesterone and duration of the luteal phase of the cycle could be seen [1-4].

LUF is found in 4.9-10% of menstrual cycles of normal fertile women [5-6]. A higher incidence has been reported in infertile women [1]. The range is between < 5% to about 20% of stimulated cycles [7].

The occurrence of LUF has been linked to many conditions, such as unexplained infertility, endometriosis, pelvic adhesions and the use of nonsteroidal anti-inflammatory, drugs (NSAIDs) [1,8-14].

The implication of the syndrome to infertility problem ranges from being an infrequent, sporadic phenomena and an uncommon cause of infertility in regularly cycling infertile women[5] to a recurrent phenomena in about one third of cases [15].

The incidence of LUF in stimulated cycles was reported to be 31.8% by Zhu (1989) [16] and 63% of LUF patients had recurrences and that LUF syndrome is of particular importance in unexplained infertility.

However, to our knowledge, no extensive studies were found on the prevalence of LUF in stimulated anovulatory and superovulated ovulatory infertile women, nor studies on the influence of stimulation protocol on the incidence of LUF.

The aim of the present study was to determine the prevalence of LUF among infertile women and the effect of stimulation protocol on its development.

PATIENTS & METHODS

A total of 300 cycles were monitored in 228 patients for different causes of infertlity. Various protocols were employed. Of all cycles, 55 were natural cycles, the remaining 246 were stimulated using clomiphene citrate (CC)/HCG, or CC plus HMG/HCG, or HMG/HCG stimulation protocols. After baseline postmenstrual evaluation serial monitoring employing TVS was started from midfollicular phase (days-5) to near midluteal phase or sonographic evidence of ovulation which is earlier (days+5) (The day of HCG trigger of ovulation being cycle day zero). MLP was measured on day +7. TVS evidence of LUF was persistence of unruptured preovulatory follicle(s) up to day+5 together with biochemical evidence of luteinization (MLP ≥1 ng/mL, the lower limit of serum progesterone for ovulatory cycle in our lab). Luteal phase length was measured to identify short luteal phase defect. Cycle outcome in terms of positive or negative serologic pregnancy test was recorded whenever available.

RESULTS

As shown in Table (I) 228 cases underwent 300 cycle monitoring giving average cycle number of 1.3% per patient. Although 76% of cycles were non-repeat (Table II), the remaining cycles were repeated ranging from 2 to 5 times. The indication for monitoring was infertility in most of cases. As seen in

Table (V), 55 cycles (18% of all) were natural, 100 (33.3%) were CC/HCG stimulated and 135 (45%) were CC+HMG/HCG stimulated and 10 (0.03%) were HMG/HCG stimulated. The method of stimulation was chosen according to the cause of infertility and method of treatment. For example cases of PCO were usually started by CC/HCg, and if resistance to CC is encountered the case was shifted to Cc+HMG/HCg. HMG only treatment was given to minority of cases in which CC+HMg failed to produce follicular growth.

As seen in Table (V) overall prevalence of LUF is 27 cases out of 300 cycles giving overall 9% prevalence of LUF. However when computed in subgroups according to stimulation protocol CC/HMG protocol had the highest value (16%), significantly higher than other groups (P=0.03).

When evaluating LUF cycles and normal ovulatory cycles (in which TVS and biochemical evidence of ovulation was fulfilled) (Table VI) it was found again that among the variables evaluated (age, BMI, stimulation method) CC/HCG protocol was employed in significantly higher proportion of cases (P=0.0001).

Although CC/HCG was used in nearly similar ratios of repeat and non repeat cycles (Table VII) LUF recurred only in 2 cycles in same patient giving recurrence rate of 2.8% of LUF cycles.

Table I :

Parameter	Value
No. of cases	228
Total cycles monitored	300
Cycles/patient	1.3
Age (Mean ± SD)	24 ± 5.4
BMI (Mean ± SD)	28 ± 3.5
Indication for monitoring primary infertility (%)	47
Secondary infertility (%)	29
PCO & infertility (%)	96

Table II : Number of patients per number of cycles monitored.

Cycles monitored	No. of patients	Value
1 cycle	230	76
2 cycles	54	18
3 cycles	11	3.6
4 cycles	4	1.3
5 cycles	1	0.3

Table III : Causes of infertility.

Causes	No.	%
Male subfertility	35	11.7
PCO	261	87
Combined Male & Female	296	98
Unexplained	4	1.3

Table IV : Types of Infertility.

Type	No.	%
Primary	180	60
Secondary	120	40

Table V : Stimulation protocol and prevalence of LUF.

Stimulation method	Cycles with rupture follicle(s)	LUF N %
Natural cycles	55	2 (3.6)*
CC/HCG	100	16 (16)*
CC+HMG/HCG	135	8 (5.9)*
HMG/HCG	10	1 (0.1)
Total	300	27 9

* Chi square 8.01 at DF3, P = 0.03

Table VI : Features of LUF cycles vs. normal ovulatory cycles.

Parameter	LUF n = 27	Normal n = 243	P
Age (mean ± SD)	26.0 ± 5.04	24.7 ± 7.07	0.26
BMI (mean ± SD)	28.9 ± 6.5	28.8 ± 4.5	0.95
CC/HCG (%)	48	18	0.0001
CC, HMG/HCG or HMG/HCG (%)	40	36.9	0.07

Table VII : CC use and Recurrent LUF.

Parameter	CC use N %	LUF N %
First Cycle (228)	154 35	25 10*
Repeat cycle (70)	49 34	2 2.8*
All cycles (300)	100 33	27 9

* P = 0.04

Table VIII : Cycle outcome in LUF cycles vs normal ovulatory cycles.

Parameter	LUF n = 27	Normal n = 243	P
Midluteal P (mean ± SD)	9.1 ± 5.9	21.9 ± 12.12	0.000
Luteal phase length (mean ± SD)	14.3 ± 2.7	15.7 ± 2.5	0.09
MLP < 10 ng/ml (%)	60	0	
Cycle pregnancy rate	0	21%	

Test statistics : cycle protocol vs LUF.

	Presence of LUF	Cycle of protocol
Chi-square	2.334	6.705
DF asymptomatic	2	2
Sig.	.311	.035

a. Kruskal Wallis test

b. Grouping variable : BMI type

Type of protocol* presence of LUF crosstabulation count.

	Presence of LUF		Total
	Absent	Present	
Type of antiestrogen	154	26	180
Protocol	56	3	59
Total	210	29	239

Chi-square test.

	Value	DF	Asymp. Sig. (2-sided)	Exact sig. (2-sided)	Exact sig. (1-sided)
	3.651	1	.056		
	2.826	1	.093		
	4.281	1	.039		
				.066	.039
	3.636	1	.057		
				.001	
	239				

a. Computed only for a 2 x 2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 7.16

c. Binomial distribution used.

DISCUSSION

LUF or absence of oocyte expulsion from primary follicle or failure of ovulatory follicle to rupture despite normal indices of ovulation is quite a common problem in the field of gynecological practice [17-18].

Although LUF is found in 4.9-10% of menstrual cycles of normal fertile women [6] a higher incidence has been reported in infertile women and ranges between 5 to 23% of stimulated cycles [7].

To our knowledge there are no wide-scale studies on the prevalence of LUF in stimulated anovulatory and superovulated ovulatory cycles in infertile women in our locality and also no studies on the value and effects of different stimulation-protocols on the incidence of LUF.

The aim of he present study was to determine the prevalence of LUF among infertile woemn and the effect of different chosen stimulation protocols on its development.

The diagnosis of LUF was undertaken by transvaginal ultrasound which is acccepted to be the method of choice for diagnosing LUF [2] together with biochemical evidences of luteal phase defect [19].

The incidence of LUF in the present study was found to be 9% (Table V). This is much lower than that reported by Qublan et al. (2006) [20] where one fourth of their series had LUF. It is also lower than that of Temmerman et al. (1984) [21] where 11.8% of their series had LUF. However, the present incidence of LUF in our series are higher than those of Hamilton et al. (1985) [2] and Luciano et al. (1990) [22] where the incidence of LUF were only 6.7% and 6% respectively.

The variabilities in the prevalence of LUF in most studies could be due to differences in the subjects studied and he variabilities of their infertility status and/or to the differences in stimulation protocols. Koninckx and Brosens (1982) [9] concluded that LUF occur more frequently in cases of unexplained inferility. Luciano and associates (1990) [22]. Bateman et al. (1990) [23] reported that 20% of patients treated with clomiphene citrate (CC) had LUF.

In the present study, the prevalence of LUF varied according to the stimulation protocol (Table V), being 3.6% of natural cycles, 16% in CC/HCG and 5.9% in CC HMG/HCG and only 0.1% in HMG/HCG. The very high incidence of LUF with the CC/HCG protocol raises the possibility of implication of clomiphene citrate in the pathogenesis of LUF by central or local actions [24-27].

The incidence of LUF with HMG/HCG stimulation was very low (0.1%) (Table V) being even lower than that observed with the natural cycles (3.6%). This is in contrast to Martinez et al. (1991) [28] who stated that LUF is more frequent with stimulated cycles. However, Check et al. (1986) [29]; Check et al. (1992) [30] demonstrated that beneficial effect of adding HMG to HCG for patients having LUF with only HCG stimulation.

In the present study, although PCOS accounted for 87% of the studied cases (Table III) yet the incidence of LUF was relatively low (9%) in comparison to the finding of Shi et al. (2006) [31] who reported 32% incidence of LUF in PCO and postulated the role of metformin and COC also laparoscopy in decreasing this high incidence.

Chen et al. (2008) [32] found that not only antimullerian hormone level, but also obesity, insulin resistance and/or elevated androgen level may relate to the development of PCOS. In the present study the BMI showed insignificant difference between cases with and those without LUF cases (Table VI).

In the present work, the mean MLP was significantly lower in LUF compared to normal

ovulatory cycles (9.1±5.9 vs 21.9+12.12 ngm/ml) respectively (P<0.001) and 60% of cases with LUF had mean MLP <10 ngm.ml (Tabe VIII). This is in agreement with Hamilton et al. (1987) [19] who advised serial TVS in infertile cases with lowered MLP.

The recurrence rate of LUF in the present study was low (2.8%). This is in accordance with Kerin et al. (1983) [5]; aksel (1987) [33]; Luciano et al. (1990) [22] who emphasized that LUF have no recurrence rate whatsoever, but is against Liukkomen et al. (1984) [15] who reported recurrence rate in one third of their cases. Temmerman (1984) [21] also reported a 95% recurrence rate, and in Zhu (1989) [16] series the recurrence was 63%. The very low recurrence rate in the present work may be explained by the fact that the cause of infertility in our series is mainly PCOS (Table I, III).

In summary, the incidence of LUF syndrome in our series is 9% in stimulated and unstimulated cycles of infertile women with PCO (96%). The incidence of LUF varies widely, according to the stimulation protocol being highest among the CC/HMG group and the possible implication of CC in the etiology of LUF is accepted.

The lowest incidence of LUF which was observed among the HMG/HCG group (0.1%) encourage such stimulation protocol for cases liable to develop LUF or recurrent cases and those with unexplained infertility. Serial TVS is recommended in stimulation protocols especially if MLP<10 ng/ml.

The value of leuprolide acetate in HCG failure[34] and also the value of anticoagulant heparin in LUF [35] waits further studies.

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