

# Luteinized unruptured follicle syndrome: incidence and recurrence rate in infertile women with unexplained infertility undergoing intrauterine insemination

H.Qublan<sup>1,3</sup>, Z.Amarin<sup>2</sup>, M.Nawasreh<sup>1</sup>, F.Diab<sup>1</sup>, S.Malkawi<sup>1</sup>, N.Al-Ahmad<sup>1</sup> and M.Balawneh<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynaecology, Prince Rashid Hospital, Royal Medical Services, Irbid, Jordan and <sup>2</sup>Department of Obstetrics and Gynaecology, Jordan University of Science and Technology, Irbid, Jordan

<sup>3</sup>To whom correspondence should be addressed at: Irbid-Aidoun, P.O. Box 97, Irbid 21166, Jordan. E-mail: hqublan@yahoo.com

**BACKGROUND:** The objective of this study was to determine the incidence and recurrence rate of luteinized unruptured follicle (LUF) syndrome in women with unexplained infertility undergoing intrauterine insemination (IUI). **METHODS:** A total of 167 women with unexplained infertility who underwent 292 cycles of IUI were enrolled in the study. All patients were treated with clomiphene citrate, 50–150 mg/daily from day 5 to 9 of their menstrual cycle. Ultrasound examination to confirm ovulation was performed on the day of IUI (day 0) and every day thereafter for another 3 days (days 1, 2 and 3). A total of 69 women who failed to conceive in the first cycle and 56 women who failed to conceive in the second cycle underwent second and third cycles, respectively. **RESULTS:** Of the total 167 patients who underwent first cycle, 42 (25%) had LUF. The incidence of LUF was 56.5% in 69 patients who underwent a second cycle of IUI treatment, of whom 33 patients had LUF in the first cycle with recurrence rate of 78.6%. In 56 patients who underwent 3 consecutive cycles, the incidence of LUF was 58.9% and recurrence rate of 90%. No pregnancies were recorded in patients with LUF during the study period. **CONCLUSION:** The incidence and recurrence rate of LUF are significantly increased in subsequent cycles of IUI. In these patients, other options of infertility treatment might be justified.

*Key words:* intrauterine insemination/luteinized unruptured follicle syndrome/pregnancy rate/unexplained infertility

## Introduction

Luteinized unruptured follicle (LUF) syndrome is defined as a 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 LH. In such cases, normal production of progesterone and duration of the luteal phase of the cycle could be seen (Marik and Hulka, 1978; Hamilton *et al.*, 1985; LeMaire, 1987). This form of anovulation is considered a subtle cause of female infertility (LeMaire, 1987). LUF is seen in 10% of menstrual cycles of normal fertile women (Killick and Elstein, 1987). A higher incidence has been reported in infertile women (Marik and Hulka, 1978). The occurrence of LUF has been linked to many conditions such as unexplained infertility, endometriosis, pelvic adhesions and the use of non-steroidal anti-inflammatory drugs (NSAIDs) (Marik and Hulka, 1978; Katz, 1988; Akil *et al.*, 1996). LUF has been demonstrated in both spontaneous and stimulated cycles (Craft *et al.*, 1980). We conducted this study to determine the incidence and recurrence rate of LUF in infertile women with unexplained infertility undergoing intrauterine insemination (IUI).

## Patients and methods

This study was carried out prospectively between September 2004 and July 2005. A total of 167 infertile women with unexplained infertility were enrolled for IUI after clomiphene citrate treatment for ovulation induction. The investigations included seminal fluid analysis, hysterosalpingogram, thyroid function test and determination of FSH, LH, androgen and prolactin concentrations. These had to be within the normal range before IUI was commenced. Clomiphene citrate was administered in doses ranging from 50 to 150 mg/daily starting from day 5 through day 9 of the menstrual cycle. Patients with clomiphene citrate resistance, hyperprolactinaemia, endometriosis, ovarian cyst detected by ultrasound on day 3–5 of the menstrual cycle and patients on NSAID were excluded from the study. All patients were instructed not to receive any medication during the treatment cycle other than clomiphene citrate. Transvaginal ultrasound (3.5 MHz) was performed on day 8–10 of the menstrual cycle to check follicular growth. The diameters of follicle(s) were measured in the transverse and longitudinal planes, from which the mean diameter was calculated. Follicles were measured every 2 days until reaching a diameter of 14 mm; thereafter, daily measurements were performed. When the follicular diameter reached  $\geq 18$  mm, 10 000 IU of HCG was administered intramuscularly, and IUI was performed 34–40 h later. Ultrasound examination was repeated on the day of IUI, which was considered day 0. This was repeated every 24 h for up to a total of 3 days (days 1, 2 and 3).

Ovulation was diagnosed based on the disappearance or shrinkage of the pre-existing follicle to at least half its original size, with obvious accumulation of free fluid in the pouch of Douglas. LUF was diagnosed if there was no evidence of ovulation after performing four consecutive ultrasonographic examinations. When the patient had more than one follicle on ultrasound, LUF was considered in the absence of any evidence of follicular rupture of all follicles. IUI was performed in all patients from 34 to 40 h after HCG administration regardless of the follicular condition. Patients who developed LUF were informed about the diminished chances of conception.

LH was checked daily starting from the day of HCG administration and 4 days thereafter to confirm the LH surge. Serum progesterone was measured 1 week after insemination. All hormonal assays including FSH, LH, estradiol (E<sub>2</sub>) and progesterone were performed in all patients by standard RIA kits (Diagnostic Product Corporation, Los Angeles, California, USA).

## Results

Demographic data of 167 infertile women who underwent 292 cycles of IUI are summarized in Table I. The average age of patients was 29 ± 4.8 years, with a range of 19–43 years. The average duration of infertility was 6 ± 3.3 years, with a range of 2–17 years. Of the total, 114 patients (68.3%) were suffering from primary infertility and 144 patients (86.2%) had regular menses. Hysterosalpingography demonstrated bilateral patent fallopian tubes in 152 of 167 (91%) and patent right or left tube in 7 (4.1%) and 8 (4.8%) patients, respectively.

Regarding the dose of clomiphene citrate, there were 14 patients on 50 mg, 147 patients on 100 mg and six patients on 150 mg. The incidence and pregnancy rates in 167 infertile women who underwent a single cycle of IUI are summarized in Table II. Rupture of the ovarian follicle(s) was confirmed in 125 patients (74.9%) with pregnancy rate of 13.6% (17/125). The absence of follicular

**Table I.** Demographic data of the study group

Characteristics	Number of patients
Age (years)	29.2 ± 4.8
Gravidity	1.7 ± 0.6
Parity	1.3 ± 0.6
Types of infertility	
Primary [n (%)]	114 (68.3)
Secondary [n (%)]	53 (31.7)
Menstrual cycles	
Regular [n (%)]	144 (86.2)
Irregular [n (%)]	23 (13.8)
Fallopian tubes	
Patent both tubes [n (%)]	152 (91)
Blocked right tube [n (%)]	8 (4.8)
Blocked left tube [n (%)]	7 (4.1)

Total number of patients was 167.

**Table II.** Frequency of luteinized unruptured follicle (LUF) and pregnancy rate in patients with one cycle of intrauterine insemination

Cycle 1	Number of patients [n (%)]	Pregnancy rate
Ruptured	125 (74.9)	17/125 (13.6)
Unruptured	42 (25.1)	0

Total number of patients was 167.

rupture documented by vaginal ultrasound was seen in 42 (25.1%) patients. No pregnancy occurred in this group.

A total of 69 patients (of whom 33 had LUF in the first attempt and failed to conceive in the first cycle) underwent a second cycle of IUI. The incidence of LUF was 56.5%, which was significantly higher compared with that seen in the first cycle. The recurrence of LUF was observed in 33 patients of the 42 who had LUF in their first cycle with rate of 78.6%. Nine of 42 patients (21.4%) who had LUF in their first IUI cycle showed follicular rupture in the second cycle, and pregnancy occurred in two women. On the other hand, of the patients who had follicular rupture in the first cycle and failed to conceive, 21 women had subsequent follicular rupture in the second cycle with occurrence of pregnancy in five cases, while six patients showed LUF (Table III). No pregnancies occurred in patients who had LUF in the second IUI cycle.

Six patients of whom three had recurrence of LUF discontinued their treatment after completion of the second cycle.

The frequency and recurrence rate of LUF in 56 infertile women who underwent three consecutive cycles of IUI are summarized in Table IV. The incidence of LUF was 58.9%. No pregnancies occurred in these patients. Of the 30 patients who had LUF in the previous two cycles, 27 (90%) showed recurrence of the syndrome in the third cycle and three patients had follicular rupture without pregnancy occurrence. On the other hand, 14 patients who had follicular rupture in the previous two cycles showed rupture of the follicle(s) in the third cycle of which three women conceived. Four patients who had follicular rupture in the second cycle showed LUF in the third cycle. In contrast, four patients who had LUF in the second cycle showed follicular rupture in the third cycle of which one patient conceived. Comparing the hormonal levels between patients with ruptured and non-ruptured follicles, no significant

**Table III.** Frequency and recurrence rate of luteinized unruptured follicle (LUF) in patients with two consecutive cycles of intrauterine insemination

Cycle 1	Cycle 2	Number of patients [n (%)]
Ruptured	Ruptured	21 (30.4)
Ruptured	Unruptured	6 (8.7)
Unruptured	Unruptured	33 (47.8)
Unruptured	Ruptured	9 (13)

Total number of patients was 69.

**Table IV.** Frequency and recurrence rate of luteinized unruptured follicle (LUF) in patients with three consecutive cycles of intrauterine insemination

Cycle 1	Cycle 2	Cycle 3	Number of patients [n (%)]
Ruptured	Ruptured	Ruptured	14 (25)
Ruptured	Ruptured	Unruptured	1 (1.8)
Ruptured	Unruptured	Ruptured	1 (1.8)
Ruptured	Unruptured	Unruptured	2 (3.6)
Unruptured	Unruptured	Unruptured	27 (48.2)
Unruptured	Unruptured	Ruptured	3 (5.3)
Unruptured	Ruptured	Ruptured	5 (8.9)
Unruptured	Ruptured	Unruptured	3 (5.3)

Total number of patients was 56.

differences in levels of E<sub>2</sub>, luteal progesterone, basal FSH, basal LH or LH surge between the two groups were found.

## Discussion

LUF is the failure of the ovulatory follicle to rupture on ultrasound examination performed daily from day 10 to 20 of the cycle despite normal indices of ovulation (Vermesh *et al.*, 1987). Different methods have been used to predict and detect the time of ovulation. These include body basal temperature (BBT) pattern, progressive enlargement of the pre-ovulatory follicle, mid-luteal progesterone levels, cervical mucus changes and mid-cycle surge of LH levels (Moghissi, 1976; Queenan *et al.*, 1980; Seibel *et al.*, 1982; Nulsen *et al.*, 1987). Of these, only the mid-cycle LH surge was found to be the most reliable predictor (Vermesh *et al.*, 1987). Ultrasound has been demonstrated to be the method of choice for diagnosing LUF (Hamilton *et al.*, 1985). The precise mechanism by which the ovulatory follicle fails to rupture is unclear. It has been postulated that LUF is a consequence of a chronic follicular inflammatory-like reaction involving inhibition of synthesis of prostaglandins (Murdoch and Cavender, 1989). Others postulated that the aberrant prolactin release and luteal phase defect might be contributory factors in the pathophysiology of this syndrome (Kugu *et al.*, 1991). More recently, Zaidi *et al.* (1995) suggested that a primary granulosa cell defect might be the responsible mechanism for this syndrome.

The results of this study clearly illustrate that the incidence and recurrence rate of LUF were significantly increased in patients with unexplained infertility who underwent IUI after stimulation with clomiphene citrate. The incidence of LUF was reported to be varied depending on the method of diagnosis such as laparoscopic inspection of the ovaries and ultrasound or steroid hormone concentrations in peritoneal fluid (Temmerman *et al.*, 1984; Hamilton *et al.*, 1985; Bateman *et al.*, 1990). The incidence in our study (25%) was higher than that reported earlier by others (Temmerman *et al.*, 1984; Hamilton *et al.*, 1985; Kugu *et al.*, 1991). In the study of Temmerman *et al.* (1984), the incidence of LUF was 11.8%. Among 270 infertile women who underwent 600 treatment cycles, Hamilton *et al.* (1985) reported an incidence of 6.7%. More recently, in a smaller size study by Luciano *et al.* (1990) that included 50 infertile women, an incidence of 6% was reported. The higher incidence in our study compared with that reported in the above-mentioned studies might be referred to homogeneity of the population of our study in terms of cause of infertility and treatment. All patients in our study were suffering from unexplained infertility, and all were treated with clomiphene citrate followed by IUI. These observations are consistent with the previous reports (Koninckx and Brosens, 1982; Bateman *et al.*, 1990; Luciano *et al.*, 1990). Koninckx and Brosens (1982) reported that LUF occurs statistically more frequently in women with unexplained infertility than in a control group. On the other hand, Luciano *et al.* (1990) found that 20% of their patients who were treated with clomiphene citrate had LUF. Similar results were reported by Bateman *et al.* (1990). These findings raise the possibility of implication of clomiphene citrate in the aetiology of LUF by central or local action that prevents follicular rupture.

In the present study, patients were followed up for three consecutive cycles. The recurrence rate of LUF increased from 25% in the first cycle to 78 and 90% in the second and third cycle, respectively. This finding is consistent with that reported by others (Liukkonen *et al.*, 1984; Temmerman *et al.*, 1984; D'Hooghe *et al.*, 1996). Relying on the concentration of steroid hormones in the peritoneal fluid, Temmerman *et al.* (1984) reported a recurrence rate of 95% in 20 infertile women. None of their patients had received clomiphene citrate treatment. A recurrence rate of 34% in three consecutive cycles was reported by Liukkonen *et al.* (1984). In their series, the laparoscopic inspection of the abdominal cavity revealed endometriosis in 20% of patients and bilateral hydrosalpinx and adhesions in 8%. In a more recent study, D'Hooghe *et al.* (1996) performing 138 laparoscopies in the early luteal phase of 52 cycles in 32 female baboons with a normal pelvis (controls) and of 86 cycles in 21 with endometriosis reported a recurrence rate of 30% in the endometriosis group. These results are in contrast to previous studies in which the investigators emphasized that LUF is associated with normal hormonal indices with no recurrence rate in subsequent cycles (Aksel, 1987; Luciano *et al.*, 1990).

In this study, no pregnancy occurred in patients with LUF. This is in agreement with previous reports. Evaluating 220 first cycles of gonadotrophin treatment, Check *et al.* (1990) found that in 148 cycles (67.3%) the patients had ultrasonographic evidence of oocyte release and pregnancy occurred in 20 cycles (13.5%). In 56 cycles, the ovum release was indeterminate and pregnancy occurred in three women (5.3%), whereas in 16 cycles (7.3%) there was no ultrasonic evidence of ovum release and none of the patients conceived (0%). Authors in that study concluded that ultrasound diagnosis of LUF does correlate with pregnancy rate.

One of the limitations of this study is the fact that it did not have a control group; moreover, it only investigated the effect of clomiphene citrate. Further studies could investigate the incidence of LUF with different stimulation regimens.

In summary, the results of this study illustrate that the incidence and recurrence rates of LUF syndrome are increased significantly in consecutive cycles stimulated with clomiphene citrate. Possible implication of clomiphene citrate in the aetiology of the syndrome exists. In such cases, other options of infertility treatment might be justified.

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