

**INCIDENCE OF LUTEINIZED UNRUPTURED FOLLICLE IN
CONTROLLED OVARIAN STIMULATION USING RECOMBINANT
AND URINARY HCG AS OVULATION TRIGGER AND STUDY OF
ITS VARIOUS OUTCOMES.**

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ABSTRACT

Objective: 1. To study and compare the incidence of luteinized unruptured follicle in controlled ovarian stimulation using urinary HCG and recombinant HCG as ovulation trigger. 2. To study recurrence rate of Luteinized unruptured follicle. 3. To study pregnancy and miscarriage rates in women with luteinized unruptured follicles. 4. To look for additional predisposing factors other than commonly known ones which may predispose to luteinized unruptured follicles.

Design: A retrospective study

Setting: An institute based study.

Patients : 1217 women who fit the inclusion criteria were subject to controlled ovarian stimulation and were given ovulation trigger using either recombinant HCG (569 women) or Urinary HCG (648 women).

The women were further evaluated for incidence of luteinized unruptured follicle and subsequent outcomes. **Results:** 1. The incidence of luteinized unruptured follicle was 3.54% with urinary HCG and 4.04% with recombinant HCG as ovulation trigger. This was statistically insignificant. 2. The recurrence rate of luteinized unruptured follicle was 63.88% in our study. 3. Patients with PCOS had a high predisposition to develop Luteinized

unruptured follicles. 4. The pregnancy rate in women with luteinized unruptured follicle was 4.3% with a 50% miscarriage rate and this was independent of other predisposing factors for LUF

INTRODUCTION

Luteinized unruptured follicle is a complication seen both in women with regular menstrual cycles, and in women undergoing controlled ovarian stimulation (COS) and is characterized by a failure of ovulation.^[1]

In the presence of anovulation, the unruptured follicle undergoes luteinization and is accompanied by progestogenic changes such as a secretory endometrium, rise in basal body temperature, LH peak, cervical mucous changes and ultrasonographic findings such as a diffuse endometrium, absence of free fluid in the Pouch of Douglas (POD) and a failure of dominant follicle to collapse.^[2]

While literature quotes the incidence of Luteinized unruptured follicle in unstimulated cycles to range from 4.9% to 10%^[1,3], there are very few studies evaluating the incidence of luteinized unruptured follicle in women undergoing controlled ovarian stimulation.

The aim of this study was to

- 1) retrospectively analyze the incidence of luteinized unruptured follicle (LUF) in women undergoing controlled ovarian stimulation with clomifene citrate/Injection HMG/Injection recombinant FSH or a combination of the above using HCG as a trigger for ovulation induction.
- 2) To compare the incidence of LUF following ovulation trigger by urinary HCG as compared to recombinant HCG.
- 3) To study the pregnancy & miscarriage rate in patients with LUF.
- 4) To study the recurrence rate of LUF.
- 5) To look for additional predisposing factors which might predispose to the occurrence of LUF (other than the commonly known ones like endometriosis, PID, pelvic adhesions)

MATERIALS AND METHODS

Ours is a retrospective study carried out over a duration of 6 months from September 2014 to February 2015 at Genesis Fertility Centre, Pune. The retrospective study was begun after taking necessary permissions from the institutional authorities.

From 1st September 2014 to 28th February 2015 a total of 1217 women who were subject to controlled ovarian stimulation fit our inclusion criteria and were included in our study.

Inclusion Criteria for our study

- 1) Women in the reproductive age group
- 2) Women with adequate follicular reserves.
- 3) Women who developed atleast one lead follicle more than 19 mm

Exclusion Criteria

- 1) Women undergoing IVF/ICSI cycles
- 2) women undergoing natural unstimulated cycles
- 3) women with poor ovarian reserves/ premature ovarian failure
- 4) known cases of endometriosis, hyperprolactinemia, and women on antidepressants & NSAIDs.

The women who fit the inclusion criteria were subjected to ovarian stimulation by clomifene citrate 50-100 mg from Day 2/3 of menses for 5 days with or without supplementation with Inj. HMG/rFSH. The patients were called back from day 11 of menses for serial ultrasonographic guided follicular monitoring. When a lead follicle exceeded 19 mm – Human Chorionic gonadotropin (HCG) trigger was given for ovulation induction using either recombinant HCG (569 cases) or urinary HCG (648 cases). All women who were undergoing a timed natural intercourse cycle (TIC) were given urinary HCG as trigger (648 cases) as compared to women undergoing IUI cycles (569 women), where the trigger used was recombinant HCG. Women with monofollicular development undergoing TIC cycle were given urinary HCG 5000 units and those with multifollicular development were given urinary HCG 10000 units intramuscularly. All women undergoing IUI cycles were given recombinant HCG 250 micrograms subcutaneously. The women were further followed up with daily ultrasonographic monitoring till the follicle ruptured or for 5 successive follicular monitorings. Failure of a follicle to rupture even after 5 successive serial monitorings accompanied by an absence of free fluid in the POD and presence of secretory changes in the endometrium was taken as luteinized unruptured follicle.

Women with LUF were further studied and evaluated for

- a) additional possible predisposing factors which may have contributed to the condition
- b) the mode of ovulation induction in these women & the drugs used.

- c) the rate of recurrence of LUF in these women &
- d) the pregnancy and miscarriage rates in these women.

RESULTS

1) Incidence of Luteinized unruptured follicle.

Of the 1217 women undergoing controlled ovarian stimulation 569 women were given recombinant HCG as trigger and 648 women were given urinary HCG as trigger. 23 women in each group presented with LUF. This has been tabulated below

Table 1.

HCG trigger given	Total No. of patients undergoing COS given HCG trigger	No. of patients with LUF	Percentage of patients with LUF
Urinary HCG (a)	648	23	3.54%
Recombinant HCG (b)	569	23	4.04%
Total a+b	1217	46	3.70%

95% confidence interval.

2) Recurrence rate of LUF

Inclusion criteria – only those women with LUF who have had 3 or more follicular monitoring cycles with us were evaluated for recurrence. 36 women fit this inclusion criteria.

Table 2.

No. of women evaluated for recurrence (by inclusion criteria)	No. of women with recurrent LUF	% of women having recurrent LUF
36	23	63.88%

DISCUSSION

Luteinized Unruptured Follicle is a rare complication in controlled ovarian Stimulation. There are no clear studies documenting the incidence of luteinized unruptured follicles in fertile women undergoing COS with HCG trigger. In our study the overall incidence of LUF in 1217 women undergoing COS with HCG trigger was 3.7%. When using urinary HCG as a trigger the incidence was 3.54 % (23/648) as compared to 4.04% (23/569) in women being given r-HCG as a trigger. This was found to be statistically insignificant (p value 0.659) (4). Although the rate of LUF in natural cycles is quoted to be 4.9 to 10% by various studies, it would be interesting to study the rate of LUF in unstimulated cycles in our centre.

The occurrence of Luteinized Unruptured Follicles is often associated with pelvic adhesions, endometriosis, unexplained infertility, hyperprolactinemia, psychological stress and the consumption of Non Steroidal anti inflammatory drugs (NSAIDS).^[1, 5, 6]

Women who were known to have these predisposing conditions were excluded from our study & other predisposing factors were sought for. An interesting fact that comes to light is 12 out of the 46 women (26%) with LUF in our study suffered from Polycystic Ovarian Disease (PCOD). This justifies the need for further studies to establish a statistically significant correlation between PCOD and LUF.

Studies show that patients with Luteinized Unruptured follicles have a high tendency for recurrence, with one study showing a recurrence rate of 78.6%.^[1] In our study, only those women who had a total of 3 or more cycles of follicular monitoring were evaluated for recurrent LUF and 36 women met this inclusion criteria. Of these 36 women, 23 women (63.88%) showed the presence of recurrent LUF. Hence our findings are consistent with other studies.

Luteinized unruptured follicle has been known to be associated with high rates of infertility, poor pregnancy outcomes and poor live birth rates. The reasons for this are not quite clear.^[8] A major reason for this could be contributory predisposing factors such as endometriosis and hyperprolactinemia. In our study, known predisposing factors were excluded. Yet only two out of the 46 women eventually conceived with IUI or Timed natural intercourse with a pregnancy rate of 4.3%. 1 out of these 2 women eventually had an early abortion. Hence the viable pregnancy rate in our study is 2.2%. This is far lesser than the expected 10 to 15% pregnancy rate we encounter in our centre. This proves that even in the absence of predisposing factors – LUF is associated with poor pregnancy rates and high miscarriage rates. In our study, 24 out of the 46 women with LUF had shown multifollicular development on COS. 13 out of these 24 women (54.1%) showed a complete LUF, whereas 11 out of these 24 women (45.8%) showed a partial LUF (with collapse of one or more follicles).

CONCLUSIONS

Hence we can conclude that Luteinized unruptured follicle is a rare complication in controlled ovarian stimulation and is associated with a high rate of recurrence and poor pregnancy outcomes independent of predisposing factors. Also the incidence of LUF does not change with the trigger used to induce ovulation.

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