

Comparison of Laparoscopic Ovarian Drilling And Step-Up Gonadotropin Therapy on Follicular Response in Anovulatory Infertile Polycystic Ovarian Syndrome Women Undergoing Ovulation Induction Cycles – Randomized Controlled Trial



Bhavana H V, Mahey R, Jayraj AK, Kumari A, Kachhawa G, Tomar S, Negi A

Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India



Introduction

- Polycystic ovary syndrome (PCOS): Most common endocrinopathy affecting 4-18% of reproductive age women
- Prevalence of PCOS in India: 3.7 to 22.5% (1)
- Accounts for 75% of women presenting with anovulatory infertility (2)
- Treatment of infertility in PCOS(3):
 - Optimize lifestyle and preconception health
 - First line agent: Letrozole
 - Second line: Gonadotropin or Laparoscopic ovarian drilling
 - Third line: In vitro fertilization

Objectives

- Primary objective**
- To study effect of laparoscopic ovarian drilling(LOD) on follicular response in anovulatory infertile PCOS women resistant to Letrozole(5mg)+low dose Human menopausal Gonadotropin(HMG)
- Secondary objective**
- To compare the two groups in terms of :
 - Gonadotropin requirement for follicular response
 - Time to conception (months)
 - Clinical pregnancy rate/ongoing pregnancy rate/live birth rate
 - To study the effect of laparoscopic ovarian drilling (LOD) on the following parameters (after 1-2 months):
 - Hormonal parameters (AMH, serum testosterone)
 - Metabolic parameters (Fasting insulin, fasting blood sugar, HOMA-IR, lipid profile)

Materials and Methods

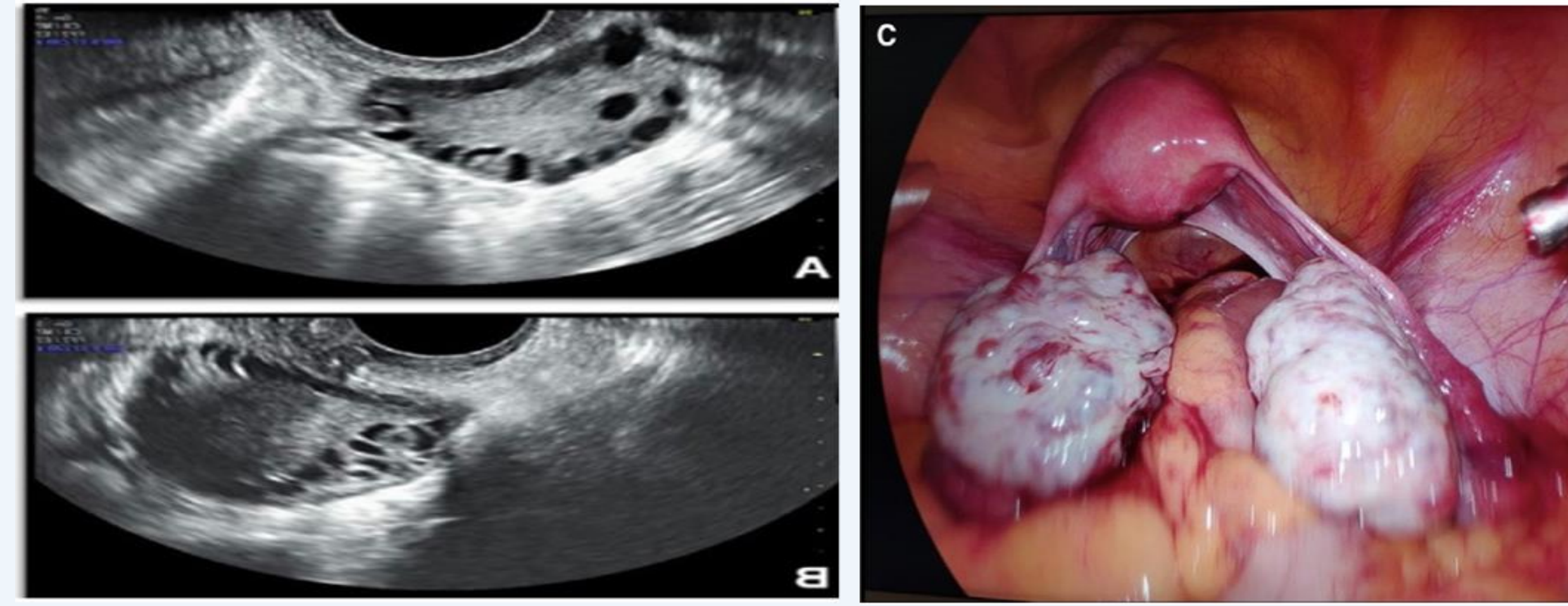
- Study design: Open-labelled pilot randomized controlled trial
- Study site: Department of Obstetrics & Gynaecology, AIIMS, New Delhi
- Study duration: May 2023 to May 2024
- Sample size: A pilot sample size of 70 (35 in each group)
- Started after ethical approval (IECPG-138/23.03.2023, RT-10/20.04.2023)
- Recruitment started after CTRI registration = 2023/04/052083

Inclusion criteria

- PCOS women with anovulatory infertility (Phenotype A,B and D)
- No follicular response to Letrozole 5mg+ HMG till day 14
- Age 22-38 years
- AMH levels > 6ng/ml
- BMI ≤ 35kg/m²

Exclusion criteria

- AMH ≤ 6ng/ml
- BMI > 35kg/m²
- Moderate to severe male factor infertility
- Endometriosis

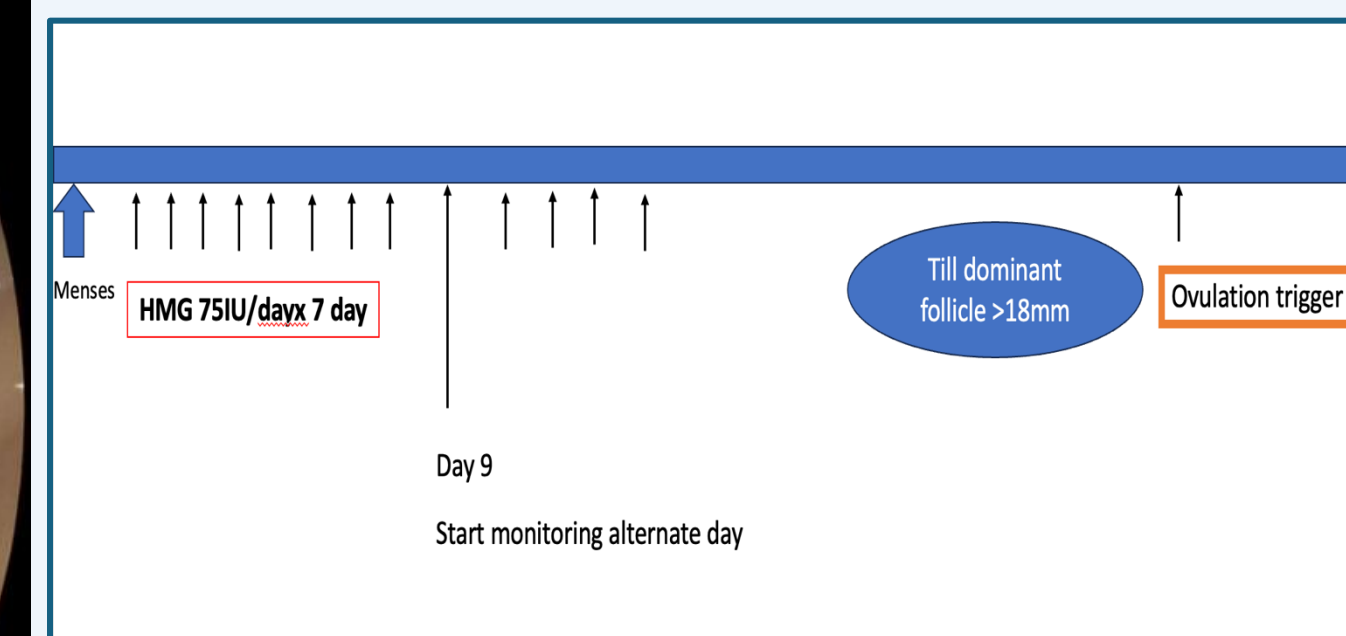


- Seventy women were randomized into done as per the computer based randomization table:
 - Group 1 (N=35):** LOD followed by 3-4 ovulation induction (OVI) cycles with Letrozole 5mg(+/- HMG) from next menstrual cycle
 - Group 2 (N=35):** Step-up Gonadotropin therapy with 75IU from day 2 of menses and follicle monitoring from day 8/9 and further step-up was done
- All LOD procedures were done by single surgeon and 4-5 punctures were made on each ovary with unipolar cautery. In women who underwent LOD, hormonal and metabolic parameters were repeated after 1-2months of procedure

Group 1: LOD



Group 2: Step Gonadotropin based OVI



Results

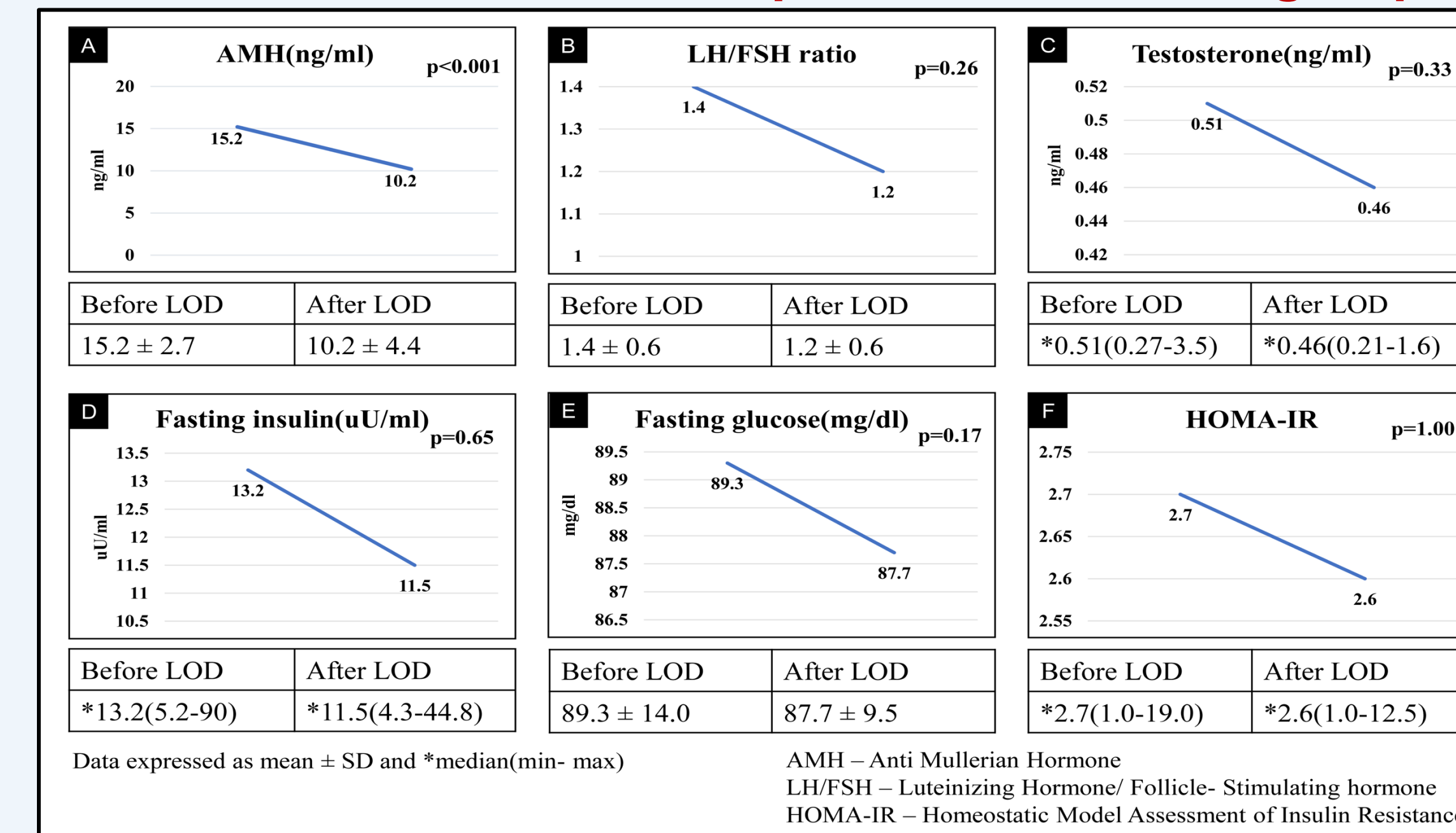
- Majority of the study participants (82.85%) were PCOS phenotype A
- Baseline clinical, hormonal, metabolic characteristics and phenotype distribution were comparable in both the groups
- Mean AMH levels in Group 1 were 15.2 ± 2.7 ng/ml and 14.2 ± 3.1 ng/ml in Group 2 (P=0.20) and follicle number per ovary(FNPO) 37.0 (Group 1) and 35.2 (Group 2) (P=0.61)

Final reproductive outcomes

Final OVI outcome	Group 1- LOD	Group 2 – Step-up Gonadotropin (Gn)	P value
Total follicular response	93.5%(87/93)	11/39(28.2%)	<0.001
Total Gn (IU)*	0(0-2700)	1050(600 -3600)	<0.001
Total cost of Gn (INR)*	0(0-18000)	7000(4000-24000)	<0.001
Clinical pregnancy rate	51.4%(18/35)	8.6%(3/35)	<0.001
Miscarriage rate	16.7%(3/18)	100%(3/3)	<0.001
Time to conception (months)*	3.9(0-8.4)		
Ongoing pregnancy rate	42.9%(15/35)	0/35(0%)	<0.001
Live birth rate	13 delivered till now 2ongoing (under follow up)	0	<0.001

Values expressed in n% *median (min-max)

Hormonal and metabolic parameters in LOD group



No significant difference seen in lipid profile after 1-2 months of LOD

Discussion

- Severity of PCOS is increasing with rising incidence of metabolic dysfunction
- A handful of patients with high AMH, AFC, and hyperandrogenism fail to respond even to Letrozole + Gonadotropin
- Step-up Gonadotropin therapy is expensive and increases the risk of multiple pregnancy and OHSS
- LOD improves ovulation rates and response to ovulation induction agents in resistant infertile PCOS women

- The utility of LOD has declined due to concerns over its invasiveness and reports of reduced ovarian reserve, possibly from excessive cauterisation or poor case selection with low follicular pool (4,5)
- LOD may be considered second-line alternative: it ensures long-lasting improvement in hormonal milieu and reduces AMH levels, which enhances follicular response, lowers Gonadotropin requirements, and decreases risks of multiple pregnancy, OHSS and reduces clinical visits and work absenteeism which may contribute to its cost-effectiveness

Strengths and limitations of the study

Strengths

- First well designed RCT from Indian-Asian PCOS women comparing LOD versus step-up Gonadotropin in patients who fail to respond to CC/Letrozole+ Gonadotropin based cycles
- All LOD procedures were done by same surgeon
- Complete follow up available

Limitations

- Single center study
- Small sample size

Conclusion

- Laparoscopic ovarian drilling (LOD) significantly improves the follicular response as compared to step-up Gonadotropin based ovulation induction and results in higher clinical and ongoing pregnancy rate along with significant reduction in Gonadotropin requirement
- LOD may be considered for PCOS women resistant to sequential letrozole + HMG-based ovulation induction especially phenotype A with high AMH and high follicle number per ovary (FNPO)

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