Dienogest vs GnRH agonists as postoperative therapy after laparoscopic eradication of deep infiltrating endometriosis with bowel and parametrial surgery

- The prevalence of endometriosis is 1.1–1.5% among women of childbearing age, and up to 10% among women suffering from pelvic pain or infertility.
- Endometriotic lesions are subject to cyclic bleeding, leading to local chronic inflammation.
- They are comparable to "wounds undergoing repeated tissue injury and repair", leading to the formation of fibrotic scars .

- Deep infiltrating endometriosis (DIE) affects 4–37% of women with endometriosis.
- Bowel DIE accounts for 12% of cases, with 90% of lesions on the rectosigmoid.
- Progestins locally inhibit the inflammatory response and induce apoptosis of endometriotic cells .
- randomized controlled trials support the use of progestins as long-time therapy, while evidence about COCs lacks.

- However, satisfactory long-term pain control has only been shown in two-thirds of patients.
- The alternative is represented by GnRH agonists, which use is limited to six months due to estrogen-deprivation symptoms.
- Laparoscopic eradication of DIE brings a significant improvement of symptoms:
- the indications are strongly debilitating symptoms, visceral damage, failure of medical therapy, and infertility.

- A nervesparing laparoscopic technique "the Negrar Method" is employed at our Institution with significantly improved outcomes on the bladder, rectal, and sexual visceral functions.
- However, pain recurrence is found in 25% of patients in the literature: the rate is 20% at 2 years and 50% at 5 years.
- A distinction must be made between symptoms and anatomical recurrence.
- Repeated surgery is necessary for 20% of patients in the literature.

- Repeated surgery faces up a more complex field, increasing the risks of complications.
- Multiple surgeries are associated with increased morbidity, health care costs, and decreased ovarian reserve: the chances of getting pregnant are halved.
- Preventing recurrence must be a crucial endpoint in the management of DIE: postoperative treatment is so recommended to prevent the regrowth of residual endometriotic cells and the development of new lesions.

Dienogest vs GnRH agonists

- Dienogest has a strong atrophying effect on endometriotic implants, associating anti-inflammatory and anti-angiogenic properties.

- At a dosage of 2 mg/day, estrogen levels are basic but not abolished: such a low estradiol level is not able to reactivate the outbreaks of endometriosis, but it is sufficient to avoid estrogen deprivation symptoms.

- Dienogest has excellent tolerability, possible adverse effects are spotting, mood disorders, headache, acne, nausea, and weight gain.
- In four RCT, Dienogest was well tolerated with a good safety profile.
- Adverse effects were headache, breast discomfort, acne,and mood disorders, each occurring in less than 10%, all of the mild-to-moderate intensity, and associated with a low discontinuation rate.
- Spotting was well tolerated, and 0.6% only reported that as the reason for premature discontinuation of Therapy.

- Previously published data encouraged the employ of Dienogest as an effective medical treatment for DIE showing comparable results in terms of symptoms relief to the gold-standard treatments and good compliance profile.
- No RCT in literature was today designed to confirm the long-term efficaciousness of Dienogest to maintain the patient's well-being and contemporarily preventing DIE relapses after radical surgical excision of the disease.

Aim of the study

- To compare in a prospective randomized controlled trial Dienogest to GnRH agonists as postoperative therapy following laparoscopic eradication of DIE.
- The primary outcome was to demonstrate the non-inferiority of Dienogest about the recurrence of pain.
- Secondary outcomes were evaluating treatment tolerability, side effects, imaging relapse rate, and pregnancy rate.

- From January 2016 to July 2017, 170 patients referred to the Department of Obstetrics and Gynecology, Gynecologic Oncology and Minimally Invasive Pelvic Surgery, International School of Surgical Anatomy, IRCCS Sacro Cuore Don Calabria Hospital of Negrar di Valpolicella (Verona, Italy) were enrolled.
- Eligibility criteria were age between 18 and 45 years, laparoscopic eradication of AFs stage III–IV DIE with bowel and parametrial surgery.
- Exclusion criteria were adverse reactions to prescribed drugs, thrombophilia, mood disorders, and decreased bone mineral density.

- The study protocol was approved by the Ethics Committee of our Institute.
- All patients provided written informed consent before enrollment: study protocol, intervention, and side effects were explained.
- Endometriosis-associated pain symptoms were assessed by the Visual Analogue Scale.

- Physical examination was performed through a combined ectovaginal examination.
- Each patient was evaluated with transvaginal ultrasound by sonographers skilled in DIE.
- Patients underwent laparoscopic excision of DIE with parametrial and bowel nerve-sparing surgery, according to the ‘Negrar Method’.

- The histopathological evaluation confirmed the presence of DIE in all cases, classified as stage III and IV of r-ASRM score.
- Patients were randomly assigned into two groups: 90 patients to group A (53%) and 80 to group B (47%).
- Group A received Triptorelin or Leuprorelin 3.75 mg depot intramuscular injection every 4 weeks for 6 months, beginning in the first 3 days of menses.
- Group B received Dienogest 2 mg/day for at least 6 months beginning on the first day of menses after surgical treatment, if compatible with the patient's oral feeding.
- Patients were followed up with an interview done at the end of the six months, asking about compliance to drug intake, treatment tolerability, pain improvement, and side effects.

- A second interview was done at a median of 30 ± 6 months asking about compliance to therapy, pain relapse, imaging relapse, and pregnancy rate.
- 9 patients in group A did not complete the follow-up. 11 patients in group B did not complete the follow-up, 4 others never took the therapy.
- Patients analyzed were 146: 81 in group A (55.5%) and 65 in B (44.5%). They were of comparable age and BMI, without differences in history and surgical intervention .
- The intensity of pain at 6 and 30 months was assessed by VAS.
- Treatment tolerability was evaluated with a multiple item validated questionnaire and with a Global Tolerability Scale ranging from 0 to 4 (0 ¼ not tolerable treatment, 4 ¼ very good tolerability).

- Both Dienogest and GnRH agonists were associated with a substantial reduction of pain between baseline and 6 months ($p < .001$).
- Similar results were observed at 30 ± 6 months ($p < .001$) .
- About treatment tolerability, on a scale from 0 to 4, a more atisfactory profile was reported by group B (mean score 3.1 versus 2.7, p ¼ .026) .

- Among side effects, a statistically significant higher number of patients in group B complained of spotting (27.7%), versus 1.2% in A, $p < .001$.
- As a consequence, significantly more patients in group A achieved amenorrhea (95%) than in B (80%), p ¼ .05.
- Significantly more patients in group A complained of hot flushes (86.4%) compared to B (12.3%, $p < .001$).

- No significant difference was found in headache, mood disorders, swelling, alopecia,breast tenderness, libido, or vaginal dryness. 29.2% in group B complained of symptoms relapse at 30 months, whereas 18.5% in A.
- The Fisher exact test with a 2 2 contingency table did not find a statistically significant difference in clinical relapse (the two-tailed p-value equals .1679). 10.7% had imaging relapse in group B, while 7.4% in A. Most of the imaging relapses are ovarian cysts (10 of 11 patients in group B and 6 in group A), where only one relapse of the recto-vaginal septum with suspect rectal infiltration was reported in group B.

- This difference did not reach any statistical significance (the two-tailed p-value equals .5592).
- The live birth rate was 19.7% in group A (9 patients conceiving after ART and 7 spontaneously) and 12.3% in B (1 after ART and 7 spontaneously) (p ¼ NS at the v2 test).

- The recurrence rate after conservative surgery for DIE is 50% at 5 years , with general agreement about the risks of repeated surgeries.

- In recent times many studies focused on Dienogest, which reduces endometriotic lesions volume and inflammatory activity creating a ‘local progestogenic environment,’moderately only suppressing estrogen level.

- Alternatively, Strowitzki et al. compared Dienogest to Leuprolide Acetate about pelvic pain and life quality .

- The reduction of pain was identical. A non-significative improvement in quality of life was found with Dienogest.

- Cosson et al. compared postoperative Dienogest to Triptorelin.
- No difference in terms of relapse and patients' satisfaction.
- Bleeding was more common with Dienogest and hot flashes with Triptorelin.
- Granese et al. compared postoperative Dienogest to Leuprorelin.
- Pain and quality-of-life scores were identical.
- No difference in imaging recurrence. Takaesu et al. compared postoperative Dienogest to Goserelin.

- The pain was significantly lowered with both. The recurrence rate demonstrated no significant difference. Side-effects were observed more within Goserelin. Abdou et al. compared postoperative Dienogest to LA.
- Reduction in pain was highly significant with both.
- Spotting and weight gain more common with Dienogest, hot flashes, and vaginal dryness with LA.
- A meta-analysis valued postoperative Dienogest on recurrence after surgery, compared to no treatment.
- The chances of recurrence appeared to be significantly lower with Dienogest .

- This study show that Dienogest and GnRH agonists are both associated with a highly significant reduction in pelvic pain as well as in the prevention of pain recurrence without significant difference.

- A statistically significant pain reduction was reported at 6 months and 12 months follow-up evaluation of all the considered VAS-scale items if compared to the baseline.
- These results agree with the previously mentioned studies , powering the idea that Dienogest is comparable to the gold standard therapy which is the GnRH agonists.
- About treatment tolerability, a more satisfactory profile was reported by Dienogest (p ¼ .026).

- The most common adverse effect in its group was spotting (27.7%): informing the patients about this common phenomenon may increase compliance.
- None of the patients reported discontinuation of therapy due to this symptom, so it had a minimal impact on compliance.
- This trial limitation consists of the small sample of patients analyzed. Its strengths are the homogenous pattern of patients, all subject to surgery by the same equipment, all for severe cases of DIE, and the long follow-up period.

- Dienogest is as effective as GnRH agonists in preventing the recurrence of pelvic pain after surgery. In addition, it has acceptable safety and good tolerability, being better tolerated by patients.

- GnRH agonists can be prescribed for a limited time only, while we need long-time therapy.

- . Dienogest offers a valid and well-tolerated postoperative treatment, that patients should be recommended to continue throughout their entire reproductive age, to be interrupted for seeking pregnancy only.

- Endometriosis is a die-hard enemy, but combining laparoscopic eradication of lesions with an effective postoperative therapy we can win the match.