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ORIGINAL ARTICLE

Impact of Hormonal Therapy on Endometriosis-Associated Pain and Fertility

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ABSTRACT

Introduction: Endometriosis is a chronic gynecological condition associated with severe pelvic pain and infertility. Hormonal therapy, including GnRH agonists, combined oral contraceptives (COCs), and progestins, is widely used for symptom management. However, the comparative efficacy of these treatments in pain reduction and fertility outcomes remains unclear. This study aimed to evaluate the impact of hormonal therapy on endometriosis-associated pain and fertility.

Methodology: This prospective cohort research was carried out from February 2023 to July 2023, at the department of Gynaecology and Obstetrics, Saidu Group of Teaching Hospitals, Swat and MMC General Hospital, Peshawar. Three treatment groups were created from 98 women with endometriosis diagnoses: progestins (n=33), COCs (n=32), and GnRH agonists (n=33). The Visual Analog Scale (VAS) was used to measure pain severity both at baseline and one year later. Ovulation and pregnancy rates were among the fertility outcomes that were documented. ANOVA, chi-square tests, and paired t-tests were used in the statistical analysis; a p-value of less than 0.05 was deemed statistically significant.

Results: GnRH agonists showed the greatest pain reduction (VAS: 8.0 → 1.9, $p < 0.001$) but had the highest side effects and lowest adherence (69.7%). COCs and progestins demonstrated moderate pain relief with better tolerability (VAS reduction: 7.9 → 3.2 and 7.8 → 2.9, respectively). Ovulation and pregnancy rates were highest in the GnRH group (69.2% and 53.8%) but were not statistically significant ($p > 0.05$).

Conclusion: Hormonal therapy effectively reduces endometriosis-associated pain, with GnRH agonists providing the best relief but lower adherence. Fertility outcomes showed improvement but lacked statistical significance. Further research is needed to assess long-term effects and optimize treatment strategies.

Keywords: Endometriosis, Hormonal Therapy, GnRH Agonists, Pain Management, Fertility, Combined Oral Contraceptives, Progestins

INTRODUCTION

The ectopic presence of endometrial-like tissue outside the uterus causes inflammation, fibrosis, and adhesion development in endometriosis, a persistent gynecological disorder[1]. About 10% of women of reproductive age experience it, and it is a leading cause of infertility and persistent pelvic pain[2]. Because of the condition's dependence on estrogen, lesions react to changes in hormone levels, making symptoms worse during the menstrual cycle[3]. Dysmenorrhea, dyspareunia, non-cyclical pelvic pain, and subfertility are among the serious morbidities linked to endometriosis that eventually damage the affected people's quality of life and mental health[4]. Despite its high prevalence, the pathophysiology of endometriosis remains incompletely understood, though multiple theories, including retrograde menstruation, immune dysregulation, and genetic predisposition, have been proposed.

Hormonal therapy remains a cornerstone of endometriosis management, aiming to suppress ovarian function and reduce estrogen stimulation of ectopic lesions[5]. Various hormonal treatments are available, including combined oral contraceptives (COCs), progestins, gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, and aromatase inhibitors[6]. Each therapy varies in efficacy, side effects, and impact on fertility[7]. COCs and progestins are first line options that help alleviate pain and regulate menstrual cycles, whereas GnRH analogs induce a hypoestrogenic state to shrink lesions but may cause menopausal like side effects[8]. More recently, selective progesterone receptor modulators (SPRMs) and newer GnRH antagonists have emerged as promising alternatives with potentially fewer adverse effects[9]. While hormonal therapy effectively manages pain in many patients, its role in improving fertility outcomes remains controversial, as many treatments suppress ovulation, necessitating assisted reproductive technologies (ART) for conception[10].

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Although hormonal therapy is widely used for symptom control, inconsistencies in treatment response and the long-term effects on fertility outcomes remain areas of concern. Current literature lacks a comprehensive evaluation of the differential impacts of various hormonal regimens on both pain relief and reproductive success. Therefore, this study aims to assess the effectiveness of different hormonal therapies in alleviating endometriosis-associated pain while evaluating their influence on fertility outcomes, addressing this critical research gap.

METHODOLOGY

Study Design and Setting: This prospective cohort study was conducted at the Department of Gynaecology and Obstetrics, Saidu Group of Teaching Hospitals, Swat and MMC General Hospital, Peshawar. The study spanned duration of six months, from February 2023 to July 2023.

Sample Size Calculation: The sample size was calculated using the World Health Organization (WHO) sample size calculator. Considering a confidence level of 95%, a power of 80%, and an anticipated effect size based on previous studies evaluating hormonal therapy in endometriosis, a minimum of 98 patients were required to achieve statistical significance.

Study Population and Eligibility Criteria: The study included women aged 18 to 45 years diagnosed with endometriosis through clinical evaluation, imaging (transvaginal ultrasound or MRI), and/or laparoscopic confirmation. Patients with previous surgical treatment for endometriosis, concurrent pelvic inflammatory disease, malignancy, or contraindications to hormonal therapy were excluded.

Data Collection and Treatment Groups: Participants were divided into three groups based on the prescribed hormonal therapy. The COCs group received low-dose estrogen-progestin therapy, while the progestin-only group was treated with either oral or injectable progestins. The GnRH agonist group received GnRH analogs along with add-back therapy to help mitigate hypoestrogenic side effects. Baseline demographic and clinical

characteristics, including age, BMI, pain severity (assessed using the Visual Analog Scale, VAS), dysmenorrhea, dyspareunia, and infertility status, were recorded.

Outcome Measures and Follow-Up: Patients were followed up at 3, 6, and 12 months to assess changes in pain severity and fertility outcomes. Pain reduction was measured using the VAS, while fertility outcomes were evaluated based on ovulation monitoring, conception rates, and assisted reproductive technology (ART) utilization. Side effects and patient adherence to therapy were also documented.

Statistical Analysis: SPSS version 26 was used to analyze the data. Whereas categorical data were displayed as frequencies and percentages, continuous variables were represented as mean ± standard deviation (SD). The chi-square test was employed to examine reproductive results, and the paired t-test was utilized to compare pain assessments before and after therapy. Statistical significance was defined as a p-value of less than 0.05.

Ethical Considerations: The Institutional Review Boards (IRBs) of the hospitals gave approval of the study. All subjects provided written informed permission, and patient data confidentiality was upheld for the entire trial.

RESULTS

A total of 98 women diagnosed with endometriosis were enrolled in the study. The mean age was 31.6 ± 5.4 years (range: 19–45 years), and the mean BMI was 24.8 ± 3.2 kg/m². The majority of patients (65.3%, n = 64) were in the 26–35 years age group. Regarding parity status, 42 (42.9%) had primary infertility, while 56 (57.1%) had secondary infertility. The most common symptom was dysmenorrhea (90.8%, n = 89), followed by dyspareunia (73.5%, n = 72), chronic pelvic pain (62.2%, n = 61), and menstrual irregularities (37.8%, n = 37). The mean baseline pain score on the Visual Analog Scale (VAS) was 8.0 ± 1.3. As shown in table 1.

Table 1: Baseline Characteristics of Study Participants

Characteristic	COCs Group (n=33)	Progestin Group (n=32)	GnRH Agonist Group (n=33)	p-value
Age (years)	30.8 ± 5.6	31.4 ± 5.3	32.5 ± 5.2	0.42
BMI (kg/m²)	24.6 ± 3.1	25.0 ± 3.3	24.9 ± 3.2	0.58
Primary infertility (%)	14 (42.4%)	13 (40.6%)	15 (45.5%)	0.89
Secondary infertility (%)	19 (57.6%)	19 (59.4%)	18 (54.5%)	0.83
Dysmenorrhea (%)	30 (90.9%)	29 (90.6%)	30 (90.9%)	0.99
Dyspareunia (%)	24 (72.7%)	23 (71.9%)	25 (75.8%)	0.93
Chronic pelvic pain (%)	21 (63.6%)	20 (62.5%)	20 (60.6%)	0.94
Menstrual irregularities (%)	12 (36.4%)	13 (40.6%)	12 (36.4%)	0.91

Pain severity was assessed at baseline, 3 months, 6 months, and 12 months, with significant reductions observed in all treatment groups ($p < 0.001$, repeated-measures ANOVA). The GnRH agonist group demonstrated the greatest pain reduction over time (VAS 8.0 → 1.9, $p < 0.001$). At 3 months, pain scores decreased to 4.8 ± 1.1 in the GnRH agonist group, compared to 5.6 ± 1.3 in the COCs group and 5.3 ± 1.2 in the progestin group ($p = 0.04$). By 6 months, further reductions were noted, with the GnRH group at 3.1 ± 1.0, the progestin group at 3.8 ± 1.2, and the COCs group at 4.2 ± 1.1 ($p = 0.02$). At 12 months, the GnRH group had the lowest pain score (1.9 ± 0.8), followed by the progestin group (2.7 ± 1.0) and the COCs group (3.1 ± 0.9) ($p = 0.001$). These findings indicate that GnRH agonists provided the most effective pain relief, while COCs and progestin also significantly reduced pain but to a lesser extent. As shown in table 2.

Table 2: Pain Score (VAS) Over Time

Timepoint	COCs Group (Mean ± SD)	Progestin Group (Mean ± SD)	GnRH Agonist Group (Mean ± SD)	p-value (ANOVA)
Baseline	7.9 ± 1.2	8.1 ± 1.4	8.0 ± 1.3	0.68
3 months	5.6 ± 1.3	5.3 ± 1.2	4.8 ± 1.1	0.04
6 months	4.2 ± 1.1	3.8 ± 1.2	3.1 ± 1.0	0.02
12 months	3.1 ± 0.9	2.7 ± 1.0	1.9 ± 0.8	0.001

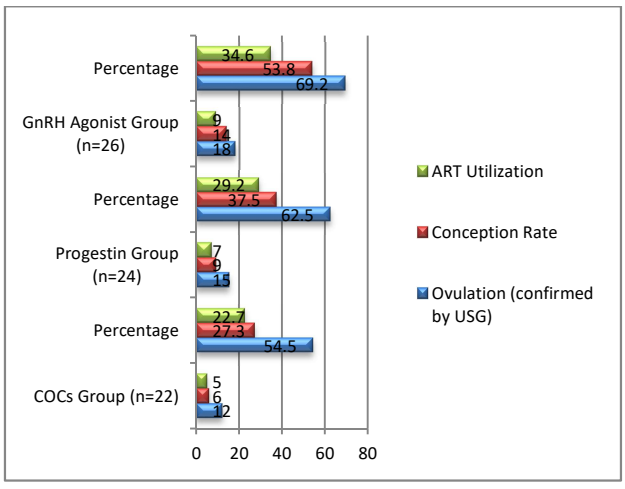

Figure 1: Fertility Outcomes among Patients Trying to Conceive

Seventy-two women who were actively attempting to conceive had their ovulation and pregnancy rates evaluated. Despite having the greatest rates of ovulation (69.2%) and pregnancy (53.8%), the GnRH agonist group did not vary statistically significantly from the other treatment groups ($p > 0.05$). Comparatively, 54.5% of women in the COCs group and 62.5% of women in the progestin group had verified ovulation ($p = 0.41$). Similarly, the progestin group had a 37.5% pregnancy rate, while the COCs group had a 27.3% pregnancy rate ($p = 0.08$). Although this difference was not statistically significant ($p = 0.56$), the GnRH group used ART at the greatest rate (34.6%), followed by the progestin group (29.2%) and the COCs group (22.7%). These results imply that although GnRH agonists had a tendency toward improved reproductive outcomes, the distinctions were not significant enough to prove that they were better than alternative hormonal treatments. as seen in figure 1.

The GnRH agonist group experienced the highest rates of hot flashes (45.5%, $p < 0.001$) and decreased libido (30.3%, $p = 0.04$), indicating a significant association between GnRH therapy and these side effects. On the other hand, the progestin group experienced irregular bleeding more often (28.1%) than the COCs group (21.2%), but this difference was not statistically significant ($p = 0.31$). Although there were mood swings in 24.2% of patients in the GnRH group, 18.8% in the progestin group, and 15.2% in the COCs group, there was no statistically significant difference between the groups ($p = 0.52$). These findings suggest that while GnRH agonists were effective in reducing pain, they were associated with more severe systemic side effects, whereas COCs and progestins had a better tolerability profile but were linked to irregular bleeding and mood-related symptoms. As shown in table 3.

Table 3: Treatment-Related Side Effects

Side Effect	COCs Group (n=33)	Progestin Group (n=32)	GnRH Agonist Group (n=33)	p-value (Chi-square)
Irregular Bleeding	7 (21.2%)	9 (28.1%)	5 (15.2%)	0.31
Hot Flashes	2 (6.1%)	4 (12.5%)	15 (45.5%)	<0.001
Mood Changes	5 (15.2%)	6 (18.8%)	8 (24.2%)	0.52
Decreased Libido	3 (9.1%)	4 (12.5%)	10 (30.3%)	0.04

Adherence to treatment varied across groups, with the COCs group showing the highest adherence rate (87.8%), followed by the progestin group (82.4%), while the GnRH agonist group had the lowest adherence (69.7%). The reduced adherence in the GnRH agonist group was primarily attributed to the higher incidence of side effects, such as hot flashes and decreased libido, which may have impacted patient compliance. As shown in figure 2.

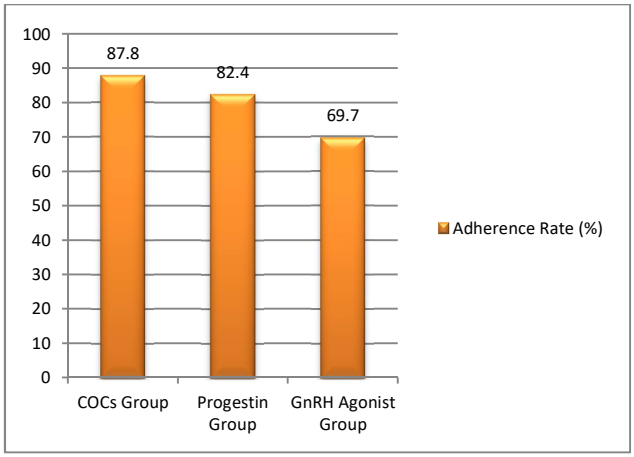

Figure 2: Adherence Rates among Treatment Groups

DISCUSSION

This study demonstrated that hormonal therapy significantly reduces endometriosis-associated pain and has a variable impact on fertility outcomes. The GnRH agonist group showed the greatest pain reduction over 12 months (VAS: 8.0 → 1.9, $p < 0.001$) but had the highest frequency of side effects, particularly hot flashes (45.5%) and decreased libido (30.3%), leading to lower adherence (69.7%). In contrast, COCs and progestin-based therapy were associated with moderate pain reduction, fewer side effects, and higher adherence rates (87.8% and 82.4%, respectively).

Fertility outcomes varied among groups, with the GnRH agonist group showing the highest ovulation (69.2%) and pregnancy rates (53.8%), though these differences were not statistically significant ($p > 0.05$). The pain reduction findings align with previous research, indicating that GnRH agonists provide superior pain relief compared to COCs and progestins[11]. However, this comes at the cost of higher adverse effects, particularly vasomotor symptoms and hypoestrogenic complications, leading to treatment discontinuation in some cases[12]. Similar studies have found that COCs and progestins, while not as effective as GnRH agonists in pain management, remain preferred due to better tolerability and compliance[13].

Regarding fertility, our findings are consistent with literature showing that GnRH agonists improve ovulation and conception rates, possibly due to their suppression of inflammation and lesion regression[14]. However, research suggests that the efficacy of GnRH agonists in enhancing fertility remains controversial, as spontaneous conception rates often remain low unless combined with assisted reproductive technologies (ART) [15]. Similar studies have reported higher pregnancy rates in progestin users compared to COCs, likely due to their endometrial-stabilizing effects[16]. In terms of adherence, our results align with existing data indicating lower compliance with GnRH agonists due to their hypoestrogenic side effects[17]. Studies suggest that add-back therapy can improve adherence and reduce bone mineral loss, a strategy that should be explored in future research[18].

Limitations and Future Suggestions: This study had certain limitations. The small sample size of 98 patients restricted the statistical power of fertility-related outcomes. The 12-month follow-up duration may not have fully assessed the long-term effects of hormonal therapy on fertility and recurrence rates. Additionally, the lack of endometriosis staging data using the ASRM staging system could have influenced treatment response. Moreover, the study did not track pregnancy outcomes beyond 12 months. Future research should include larger sample sizes, extended follow-up periods, and comparisons with surgical interventions to better understand the long-term impact of hormonal therapy on endometriosis-associated pain and fertility outcomes.

CONCLUSION

This study highlights the significant role of hormonal therapy in managing endometriosis-associated pain and fertility outcomes. GnRH agonists provided the most effective pain relief but were associated with higher side effects and lower adherence rates, whereas COCs and progestins offered moderate pain control with better tolerability. Fertility outcomes showed a trend toward improvement with GnRH agonists, though statistical significance was not achieved. While hormonal therapy remains a key treatment modality, its long-term impact on fertility warrants further investigation. Future research should explore larger cohorts, longer follow-up durations, and comparisons with surgical interventions to optimize treatment strategies for endometriosis patients.

REFERENCES

1. Resta C, Moustogiannis A, Chatzinikita E, Ntalianis DM, Ntalianis KM, Philippou A, Koutsilieris M, Vlahos N. Gonadotropin-releasing hormone (GnRH)/GnRH receptors and their role in the treatment of endometriosis. Cureus. 2023 Apr 26;15(4).
2. Vercellini P, Bandini V, Buggio L, Barbara G, Berlanda N, Dridi D, Frattaruolo MP, Somigliana E. Mitigating the economic burden of GnRH agonist therapy for progestogen-resistant endometriosis: why not?. Human Reproduction Open. 2023 Jan 1;2023(2):hoad008.
3. Vannuccini S, Clemenza S, Rossi M, Petraglia F. Hormonal treatments for endometriosis: The endocrine background. Reviews in Endocrine and Metabolic Disorders. 2022 Jun;23(3):333-55.
4. Donnez J, Taylor HS, Taylor RN, Akin MD, Tatarchuk TF, Wilk K, Gotteland JP, Lecomte V, Bestel E. Treatment of endometriosis-associated pain with linzagolix, an oral gonadotropin-releasing hormone–antagonist: a randomized clinical trial. Fertility and sterility. 2020 Jul 1;114(1):44-55.
5. Yan H, Shi J, Li X, Dai Y, Wu Y, Zhang J, Gu Z, Zhang C, Leng J. Oral gonadotropin-releasing hormone antagonists for treating endometriosis-associated pain: a systematic review and network meta-analysis. Fertility and Sterility. 2022 Dec 1;118(6):1102-16.
6. Bezhenar VF, Kruglov SY, Kuzmina NS, Krylova YS, Sergienko AS, Abilbekova AK, Zhemchuzhina TY. Effectiveness of long-term hormone therapy for endometriosis after surgical treatment. Obstetrics and gynecology. 2021 Apr 15(4):134-42.
7. Skorupskaite K, Bhandari HM. Endometriosis and fertility. Obstetrics, Gynaecology & Reproductive Medicine. 2021 May 1;31(5):131-6.
8. Capezzuoli T, Rossi M, La Torre F, Vannuccini S, Petraglia F. Hormonal drugs for the treatment of endometriosis. Current Opinion in Pharmacology. 2022 Dec 1;67:102311.
9. Samy A, Taher A, Sileem SA, Abdelhakim AM, Fathi M, Haggag H, Ashour K, Ahmed SA, Shareef MA, AlAmodi AA, Keshta NH. Medical therapy options for endometriosis related pain, which is better? A systematic review and network meta-analysis of randomized

controlled trials. Journal of gynecology obstetrics and human reproduction. 2021 Jan 1;50(1):101798.
10. Richard E, Morin J, Murji A, Lemyre M, Laberge PY, Maheux-Lacroix S. Effect of postoperative hormonal suppression on fertility in patients with endometriosis after conservative surgery: a systematic review and meta-analysis. Obstetrics & Gynecology. 2022 Jun 1;139(6):1169-79.
11. Khan Z. Fertility-related considerations in endometriosis. Abdominal Radiology. 2020 Jun;45(6):1754-61.
12. Mikuš M, Vitale SG, Ćorić M, Zajec V, Ciebiera M, Carugno J, D'alterio MN, Herman M, Puževski T, Angioni S. State of the art, new treatment strategies, and emerging drugs for non-hormonal treatment of endometriosis: a systematic review of randomized control trials. Gynecological endocrinology. 2022 Nov 2;38(11):911-7.
13. Kulyk II, Khmil SV. Endometriosis-associated infertility: the role of hormones and its correction. International Journal of Medicine and Medical Research (IJMMR). 2021 May 18;2(6):5-10.
14. Bonavina G, Taylor HS. Endometriosis-associated infertility: From pathophysiology to tailored treatment. Frontiers in endocrinology. 2022 Oct 26;13:1020827.
15. Rezende GP, Venturini MC, Kawagoe LN, Yela Gomes DA, Benetti-Pinto CL. Surgery vs. hormone-based treatment for pain control in deep infiltrating endometriosis: a retrospective cohort study. Current medical research and opinion. 2022 Apr 3;38(4):641-7.
16. Allaire C, Bedaiwy MA, Yong PJ. Diagnosis and management of endometriosis. Cmaj. 2023 Mar 14;195(10):E363-71.
17. Chen LH, Lo WC, Huang HY, Wu HM. A lifelong impact on endometriosis: pathophysiology and pharmacological treatment. International journal of molecular sciences. 2023 Apr 19;24(8):7503.
18. Khashchenko EP, Uvarova EV, Chuprynin VD, Pustynnikova MY, Fatkhudinov TK, Elchaninov AV, Gardanova ZR, Ivanets TY, Vysokikh MY, Sukhikh GT. Pelvic pain, mental health and quality of life in adolescents with endometriosis after surgery and dienogest treatment. Journal of Clinical Medicine. 2023 Mar 20;12(6):2400.

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