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Research Article

Retrospective Observational Study of a Combination of Resveratrol, N-acetylcysteine (NAC), Curcumin, and Vitamin D for the Treatment of Endometriosis and Its Recurrence

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Abstract

The search for optimal therapy for endometriosis continues, and the use of dietary supplements is gaining attention. Supplements can be employed for their anti-inflammatory, antioxidant, anti-proliferative, and immune-modulatory properties. A retrospective randomized observational study was conducted on 5017 cases, where 2814 individuals were administered a combination of Resveratrol, N-acetylcysteine (NAC), Curcumin, and Vitamin D, along with other modes of treatment, while 2203 were treated without the combination. Data on recurrence and pain resistance (determined based on feedback during each clinical visit) have been presented, analyzed, and discussed. Based on these observations, the findings suggest that dietary supplements can be used as a complementary treatment for endometriosis.

Keywords: Dietary Supplements; Complementary Therapies; Endometriosis

Introduction

Endometriosis is defined as the presence of stroma-like tissue and functional endometrial glands outside the uterus. It is an endocrine disorder that results in pelvic discomfort, dysmenorrhea, and a long-lasting inflammatory response that frequently leads to the development of adhesions in the pelvis and abdomen. Endometriosis can have major physical, sexual, psychological, and social effects and it can be a long-term condition.

While surgical interventions such as ovarian cystectomy, salpingo-oophorectomy, and total abdominal hysterectomy with bilateral salpingo-oophorectomy are often performed, recurrence rates remain high. Thus, there is a need for adjunctive therapies to complement existing treatments. Resveratrol, NAC, Curcumin, and Vitamin D have garnered attention for their potential anti-inflammatory and antioxidant properties, which may be beneficial in managing endometriosis. This is a retrospective study of the effect of a combination of Resveratrol, NAC, Curcumin and Vitamin D on endometriosis treatment and recurrence, using real-world evidence.

Endometriosis

The pathogenesis of endometriosis involves a complex interplay of endocrine, immunologic, pro-inflammatory, and pro-angiogenic processes [1]. New theories in endometriosis research suggest that immune cells, adhesion molecules, extracellular matrix metalloproteinases, and pro-inflammatory cytokines activate or alter the peritoneal microenvironment, creating conditions conducive to the differentiation, adhesion, proliferation, and survival of ectopic endometrial cells [2-5]. However, it remains uncertain whether these factors are causal or merely represent features of the pathophysiological process measured years after symptom onset. When choosing a treatment for endometriosis, it is crucial to consider the patient's predominant symptoms and preferences, age, the side-effect profile of medications, and the outcomes of possible surgery. Additionally, the extent and location of the disease, previous treatment, and cost-effectiveness should be taken into account [6,7].

Endometriosis is one of the most prevalent gynecological conditions, characterized by the growth of endometrial-like tissue (glands and stroma) outside the uterine cavity [1]. The primary symptoms of endometriosis are pelvic pain and infertility. Other common symptoms include irregular uterine bleeding, dysmenorrhea, dyspareunia, and dysuria [2,3]. Endometriosis has been seen to be prevalent in 10% women of reproductive age [4], causing pelvic pain and discomfort in 30-80% women and infertility in 10% of women with the disease [5,6]. The occurrence is highest in

those between the ages of 25 and 29 and lowest in those over 44 [7]. Before acquiring a surgical diagnosis, women typically suffer symptoms for six to twelve years [8]. Recurrences are common after both drug and surgical treatment. One study found the overall recurrence rate to be 21.5% and 40–50%, two- and five-years following surgery, respectively [9].

The most common sites for endometrial lesions include the ovaries, fallopian tubes, uterine ligaments, cervical-vaginal area, abdominal wall, umbilicus, urinary tract, and rectum [10,11]. At present, pharmacotherapy and surgical resection are the main therapeutic approaches for endometriosis. Pharmacotherapy consists of hormone therapies that induce hypoestrogenism or antagonize estrogen effects and non-hormone therapy for alleviating pain such as non-steroidal anti-inflammatory drugs (NSAIDs) [12]. Surgery is often utilized for refractory cases or infertility [13].

The initiation and development of endometriosis is affected by genetic, immunological, endocrine and environmental factors [14,15]. A close correlation of endometriosis with an elevated incidence of endometrial and ovarian malignant tumors has been reported by some studies [16,17]. Endometriosis also has adverse effects on the quality of life – sleep quality, physical and psychological wellness, sexual function and interpersonal relationships. This results in a large economic burden for individuals, the healthcare system and on society [18,19].

Diagnosis

Diagnostic methods consist of clinical examination, imaging, lab tests and surgery. Endometriosis should be suspected in reproductive-aged women with chronic and/or cyclic pelvic pain (e.g., dysmenorrhea, deep dyspareunia, dyschezia), pelvic mass (e.g., ovarian endometrioma and adenomyosis), and/or subfertility. It should also be suspected for unexplained fatigue, weariness, depression, anxiety, hematuria, rectal bleeding, and other catamenial symptoms outside the genitourinary system [1]. In the past, diagnosis heavily relied on laparoscopy. However, there are surgical risks involved and diagnosis relies on identifiable pelvic lesions rather than consideration of endometriosis as a systemic disease with variable presentations [2]. Another important consideration must be patient history, including infertility history [3,4]. Depending on the location of the lesions. physical examination findings diagnose endometriosis with high accuracy [5,6].

Recommendations around clinical diagnosis

NICE, 2017- If abdominal or pelvic examinations are normal, do not rule out the possibility of endometriosis. Referrals for additional evaluation and research should be considered if clinical suspicion persists or if symptoms continue. FOGSI, 2019- The diagnosis of endometriosis should be considered in the presence of symptoms (7 D's- Dysmenorrhea, Dyspareunia, Dysuria, Dyschezia, Dysfunctional (abnormal) uterine bleeding, Difficulty in conception, Diffuse abdominal pain. Clinicians should consider the differential diagnosis as well. ESHRE, 2022- Patients without previous sexual intercourse and/or adolescents, rectal examination can be helpful for diagnosis. Clinical examination, including vaginal examination where appropriate, should be considered to identify deep nodules or endometriomas in patients with suspected endometriosis, although the diagnostic accuracy is low.

Imaging is now considered a major component of clinical diagnosis. It helps in further investigating underlying symptoms, localizing the disease, and determining severity of disease [7]. In some cases, transvaginal sonography (TVS) improves accuracy when considered along with symptoms, patient history, and/or physical findings [8,9]. Alternative imaging approaches, such as transabdominal or transrectal sonography (TRS), may be considered where TVS is inappropriate [10]. An ultrasound evaluation should assess the mobility of pelvic organs by including the anterior and posterior pelvic compartments [11,12]. This is as suggested by the International Deep Endometriosis Analysis (IDEA) consensus [13]. Magnetic Resonance Imaging (MRI) is the imaging technique with the highest overall accuracy for assessing the extent of deep infiltrating endometriosis (DIE) [14]. Anatomic response to medical or surgical treatment is now also being increasingly evaluated using MRI [15].

Recommendations around imaging

FOGSI, 2019- TVS can be used to diagnose ovarian endometrioma. Positive soft markers such as ovaries not at the usual position, kissing ovaries, ovarian fixation to the uterus and iliac vessels, and tenderness during ultrasound examination can be used to predict endometriosis. Transvaginal ultrasound can be recommended to diagnose or rule out rectal/bladder endometriosis. NICE, 2017- Consider transvaginal ultrasound: to investigate suspected endometriosis even if the pelvic and/or abdominal examination is normal to identify endometriomas and deep endometriosis involving the bowel, bladder or ureter. If a transvaginal scan is not appropriate, consider a transabdominal ultrasound scan of the pelvis. FOGSI, 2019- Pelvic MRI is not recommended as the primary investigation to diagnose endometriosis in women with symptoms or signs suggestive of endometriosis. MRI is recommended when USG examination is not suggestive or when there is deep infiltrating endometriosis, and patient requires extensive surgery or to rule out malignancy as it can characterize the lesion. NICE, 2017- Do not use pelvic MRI as the primary investigation to diagnose endometriosis in women with symptoms or signs suggestive of endometriosis. Consider pelvic MRI to assess the extent of deep endometriosis in-

volving the bowel, bladder, or ureter. Ensure that pelvic MRI scans are interpreted by a healthcare professional with specialist expertise in gynecological imaging. ESHRE, 2022- Strong recommended that in women with suspected endometriosis, further diagnostic steps, including imaging, should be considered even if the clinical examination is normal. Clinicians should not use measurement of biomarkers in endometrial tissue, blood, menstrual or uterine fluids to diagnose endometriosis. Clinicians are recommended to use imaging (US or MRI) in the diagnostic work-up for endometriosis, but they need to be aware that a negative finding does not exclude endometriosis, particularly superficial peritoneal disease.

Laboratory tests

CA-125 is used as a biomarker for diagnosing endometriosis, but its usefulness is limited. This is because CA-125 levels can be elevated in a variety of situations, including uterine fibroids, adenomyosis, acute pelvic inflammatory disease, ovarian cysts, pancreatitis, chronic liver disease, menstruation, and pregnancy. However, if CA-125 levels are above 35 U/ml, endometriosis is likely present. At this time, the positive predictive value was 0.58 and the negative predictive value was 0.96. Therefore, CA-125 can be used as an auxiliary test for diagnosing endometriosis, and if CA-125 levels are high in symptomatic patients, the diagnosis of endometriosis can be considered [16].

FOGSI, 2019- CA - 125 is not a specific biomarker for endometriosis. It is not recommended for routine clinical use. In some cases it may be of value for treatment follow-up. NICE- 2017- Do not use serum CA125 to diagnose endometriosis. If a coincidentally reported serum CA125 level is available, be aware that: a raised serum CA125 (that is, 35 IU/ml or more) may be consistent with having endometriosis. Endometriosis may be present despite a normal serum CA125 (less than 35 IU/ml).

Treatment and management

Both medical and surgical therapies are used for endometriosis treatment. Non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics may be used for pain management, either as monotherapy or in combination with other treatments [1]. In addition, pharmacological hormone therapy may be used in the form of contraceptives, progestogens, and gonadotrophin-releasing hormone [GnRH] agonists or antagonists [2].

Age, history, side-effects profile, extent of lesions and locations and preliminary treatments are considered in order to decide on a treatment strategy [3,4]. Patients who do not respond to pharmacological treatment may need surgical intervention. Surgery is found to be a clinically effective solution followed by long-term pharmaceutical therapy with NSAIDs and oral contraceptives [5,6]. However, therapeutic agents like NSAIDs have shown short- and long-term adverse effects, especially on the gastrointestinal and cardiovascular systems and this restricts their use on many patients with endometriosis [7,8].

There is a growing interest in dietary supplements as a complementary treatment. Studies show that lower levels of vitamin D, zinc, and vitamin E, carry a greater risk for endometriosis. Magnesium, curcumin, resveratrol, and ECGC were beneficial in animal studies due to their antiangiogenic effects Omega 3 and alpha-lipoic acid improved endometriosis-associated pain in human studies. Curcumin, omega 3, NAC, vitamin C, and ECGC supplementation decreased endometriotic lesion size in animal and human studies. Curcumin, omega 3, and NAC were found to prevent disease pathogenesis or recurrence in animal studies [9]. Polyphenols may represent new therapeutic agents for the treatment of endometriosis aimed at improving the living conditions of women affected by this disease. The use of polyphenolic compounds for endometriosis treatment has no negative effects on fertility, reproductive organs and development of offspring; moreover, it is more convenient than the use of conventional treatment and turns out to be more suitable for long-term treatment [10]. The oxidative stress status may represent the key to controlling the disease. In this context, the anti-inflammatory, antioxidant, or antitumor potential of selected polyphenols or vitamins can be used as an inexpensive and readily available means for preventing and treating endometriosis [11].

A review of existing literature on the effects of Resveratrol, NAC, Curcumin, and Vitamin D on the pathophysiology of Endometriosis.

Resveratrol

Resveratrol, a natural product, is mainly found in grapes and red wines, and it also exists in some other plants and several genera of microorganisms. Based on in vitro, animal, and clinical studies associated with endometriosis, Resveratrol has been reported to have multiple biological functions, such as anti-proliferative, pro-apoptotic, anti-angiogenic, anti-oxidant, anti-invasive, and anti-adhesive effects [1]. The hallmark of inflammation in endometriosis is over-activation of matrix metalloproteinases (MMPs)and Resveratrol may help control inflammation by significantly reducing MMP-2 expression in the endometrium of endometriosis patients [2]. Treatment with resveratrol has been shown to decrease the expression of VEGF, Transforming growth factor-β (TGF-β), and MMP-9 in endometrial stromal cells from endometriosis patients and suggests that resveratrol may inhibit the progression of endometriosis [3].

N-acetylcysteine

N-acetylcysteine (NAC) has shown effectiveness in reducing endometriosis-related pain symptoms, the size of endometriomas, and the serum levels of Ca125. Furthermore, it showed a positive impact on patient fertility [30]. The mean diameter and volume of

endometriomas were found to be significantly reduced after NAC administration. Serum Cancer Antigen CA-125 levels were also significantly reduced [4].

Curcumin

Curcumin treatment was shown to suppress the inflammatory response of endometrial cells and reduce the expression of Sterol Regulatory Element Binding Protein-1 (SREBP-1). SREBP-1 is a transcription factor involved in lipid metabolism and inflammatory response, and curcumin can reduce inflammation in endometrial cells by inhibiting SREBP-1 expression [5]. An in vitro study showed that curcumin downregulated the expression of Vascular Endothelial Growth Factor (VEGF), a key angiogenic factor that promotes the growth of new blood vessels, in endometriosis cells. The inhibitory effect of curcumin on endometriosis cell survival was mediated, at least in part, through the downregulation of VEGF expression [6].

Vitamin D

Vitamin D has been increasingly recognized for its potential role in the management of endometriosis. A study by Somigliana., *et al*. (2007) found that women with endometriosis had lower serum Vitamin D levels compared to healthy controls, suggesting a potential link between Vitamin D deficiency and the development of the disease [20]. Additionally, a meta-analysis by Miyashita., *et al*. (2016) concluded that Vitamin D supplementation may help reduce the risk of endometriosis and alleviate symptoms associated with the condition [21]. The proposed mechanisms by which Vitamin D may exert its effects include modulating the immune system, reducing inflammation, and inhibiting the growth and invasion of ectopic endometrial tissue (Agic., *et al*. 2007; Somigliana., *et al*. 2007) [21,22]. Furthermore, Vitamin D has been shown to influence the expression of genes involved in the pathogenesis of endometriosis, such as those related to angiogenesis and cell [21].

Materials and Methods

EndoRecov, a nutraceutical product containing a combination of Resveratrol, N-acetylcysteine (NAC), Curcumin, and Vitamin D, was used throughout the study. This product is marketed by Edence Lifesciences. The patients were prescribed EndoRecov and purchased it themselves, without any support or reimbursement from the pharmaceutical company.

This Observational study included 5,017 patients diagnosed with endometriosis who underwent different surgical interventions, including ovarian cystectomy, salpingo-oophorectomy, and total abdominal hysterectomy with bilateral salpingo-oophorectomy. 2814 patients received the nutraceutical supplement EndoRecov as part of their treatment protocol. All patient with endometriosis were prescribed the medication. Those individuals who did not take the medications were grouped into control group. Data on pain resistance based on patient feedback during each clinical visit, parity, stages of endometriosis, and age distribution were collected and analyzed.

Results

This study examined the age distribution of the patients included in the investigation of the disease recurrence following various surgical interventions, using the nutraceutical product EndoRecov.

Table 1 in majority of the cases (1090 or 39.6%) were in the age group of 26-30 years, followed by the 20-25 years age group (960 or 34.9%) and the under 20 years age group (378 or 13.8%). The 31-35 years age group accounted for 324 cases (11.8%), while the 36-40 years and over 40 years age groups had significantly fewer cases, with 46 (1.7%) and 16 (0.6%) cases, respectively. This age distribution pattern suggests that the condition under study is more prevalent among younger individuals, particularly those in the reproductive age range.

Age	No. of cases
< 20	378
20 - 25	960
26 - 30	1090
31 - 35	324
36 - 40	46
> 40	16

Table 1: Age distribution.

The high number of cases in the 26-30 and 20-25 years age groups indicates that this demographic may be at a higher risk of developing Endometriosis. The relatively lower number of cases in the older age groups, particularly the 36-40 years and over 40 years groups, may be attributed to various factors, such as the natural progression of the condition, the effectiveness of earlier interventions, or the potential impact of hormonal changes and other age-related factors. The observed age distribution highlights the importance of early detection, prompt management, and the implementation of preventive strategies, especially for individuals in the high-risk age groups.

Most patients were diagnosed with stage I (1,651) or stage II (1,101) endometriosis, while stage III (46) and stage IV (16) were less common. The majority of patients (1,774) were nulliparous, followed by para I (619), para II (409), and para III (12). Most patients were diagnosed with stage I (1,651) or stage II (1,101) endometriosis at the time of laparoscopic surgery, while stage III (46) and stage IV (16) were less common.

Recurrence of disease

The study examined the recurrence rates of endometriosis after various surgical interventions, with and without the inclusion of the nutraceutical supplement EndoRecov. Among patients who underwent ovarian cystectomy, the recurrence rate after 1 year was 86 cases, and after 2 years, it increased to 106 cases. Patients who underwent ovarian cystectomy combined with adhesiolysis showed a lower recurrence rate, with 19 cases after 1 year and 10 cases after 2 years. The recurrence rates were even lower in the group that underwent salpingo-oophorectomy with adhesiolysis, with 21 cases after 1 year and 7 cases after 2 years. No recurrence was reported in the 18 patients who underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy.

	Cases	Recurrence after 1 year	Recurrence after 2 years
Ovarian cystectomy	1106	86	106
Ovarian cystectomy with adhesiolysis	714	19	10
Salpingo oophorectomy with adhesiolysis	976	21	7
Total abdominal hysterectomy with bilateral salpingo-oophorectomy	18	-	-

Table 2

When compared to age-matched controls who did not receive the EndoRecov nutraceutical supplement, the recurrence rates were significantly lower in the intervention groups. The recurrence rates for the control groups were 60% for ovarian cystectomy, 38% for ovarian cystectomy with adhesiolysis, and 34% for salpingo-oophorectomy with adhesiolysis. The control group that underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy had a zero-recurrence rate.

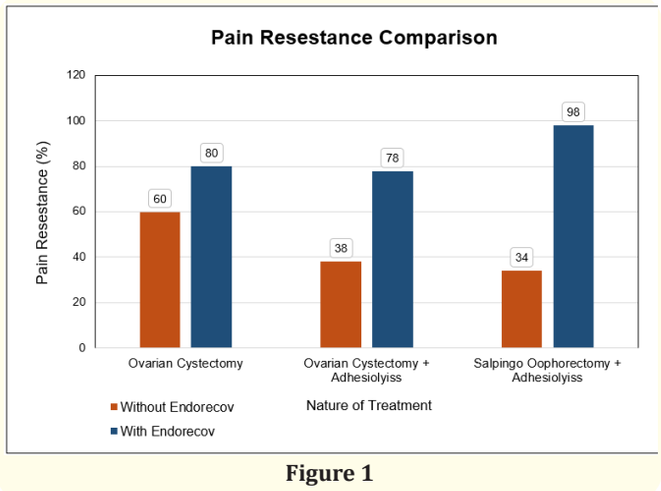

Figure 1

The study also evaluated the pain scores of patients undergoing different treatment protocols. Patients who received the combination of surgery, GnRH agonist therapy, and the EndoRecov supplement showed the greatest improvement in pain scores, with a 75% reduction at 30 days, an 80% reduction at 60 days, and 90% reduction at 90 days.

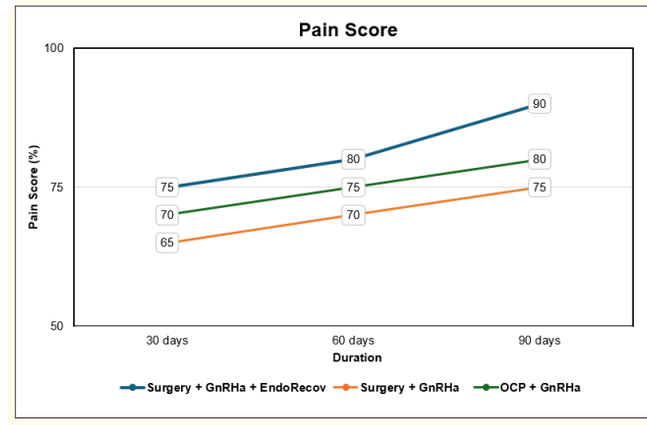

Figure 2

Patients who received post-surgery GnRH agonist therapy without the EndoRecov supplement showed a slightly lower but still significant reduction in pain scores, with a 65% reduction at 30 days, 70% reduction at 60 days, and 75% reduction at 90 days. Patients who received a combination of oral contraceptive pills (OCP) and GnRH agonist therapy also experienced a notable reduction in pain scores, with a 70% reduction at 30 days, 75% reduction at 60 days, and 80% reduction at 90 days.

These findings suggest that the integration of surgical intervention, hormonal therapy, and the nutraceutical supplement EndoRecov may provide the most comprehensive and effective approach in managing endometriosis-related pain and reducing disease recurrence.

Discussion

Endometriosis affects women belonging to the reproductive age groups. Those with no prior conceptions (nulligravida) report with complaints of discomfort and infertility, whereas, the older age group of women report with chronic pelvis pain and discomfort. In both scenarios, the quality of life is severely affected in those affected with endometriosis. There is no definitive treatment for endometriosis however there are several medical options to manage the condition. Of all the available medications, EndoRecov is a non-hormonal medical option which was available for post marketing surveillance. This observational study was done an showed

a significant improvement in the quality of life if these women as reported by them during the OPD visits.

Conclusion

This study provides valuable insights into the management of endometriosis and the potential benefits of incorporating the nutraceutical supplement EndoRecov into the treatment regimen. The findings suggest that the integration of surgical interventions, hormonal therapy, and nutraceutical supplements may provide the most comprehensive and effective approach in managing endometriosis-related pain and reducing disease recurrence. The study highlights the importance of a multifaceted treatment strategy that addresses both the surgical and medical aspects of endometriosis management.

Further research is warranted to validate these findings and explore the long-term outcomes of this integrated approach. Nonetheless, this study offers valuable insights that can guide clinicians in developing personalized treatment plans for patients with endometriosis, with the ultimate goal of improving their quality of life and reducing the burden of this chronic and debilitating condition.

Ethics Approval

Due to the nature of our study, Ethics approval was not required.

Conflicts of Interest

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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