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Reversal Processes by Dynamic Therapies: Pathophysiology, Biomarkers and Integrative Applications for Endometriosis: Case Report

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

Introduction: This study's goal was to understand the pathophysiology of endometriosis and its epigenetic biomarkers that are useful in proposing integrative therapies for improved health outcomes. Current conventional therapies have been ineffective in treating endometrial abnormalities observed in patients diagnosed with the disease.
Patient Concerns: The endogenic treatment protocol that was based on the integrated process of reversal therapy was provided to thirty female participants enrolled in the study. Resulting fertility issues due to the disease renders a significant percentage of this population nulliparous. Literature is exhausted with research to establish relative pathogenicity of the monospecific disease as it corresponds to its molecular characteristics, symptoms, and progression.
Diagnosis: Angiogenesis was found to be a characteristic mechanism during the development of endometriosis resulting from a mutation of the GnRH gene thus compromising JEG-3 cell operations. Upregulated immune-related factors and functionally prevalent angiogenesis predisposes this population to acquire abnormal endometrial outcomes.
Interventions: A monotherapeutic approach was utilized consisting of a 3 part biomedical treatment protocol applied for 90 days to obtain menstral process improvements by decreasing the incidence of endometriosis and corresponding infertility.

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Outcomes: Proposed mechanism of action provided by The Tejeda Equation (∑(σX GnRH ⇒ JEG3f)+ (σα ^βER) ∴ NR3A1 ≥ 300-437pg/ml e (τ +30dy)∆ δEEC) permitted development of applied biomedical treatment protocol Fig.4. The protocols therapeutic matrix addressed all aspects of Bis4 by reversal of the mutated GnRH gene, restoration of JEG-3 cells and diminished endometrial lesions Fig.1. Corresponding results proved favorably.
Conclusion: Some significant genetic factors that are critical contributors to endometriosis have remained undiscovered. Continued research will be pursued that can assist in developing alternate diverse treatment strategies for the affected population.

Keywords: Pathophysiology; integrative therapies; reversal therapy; epigenetic biomarkers; infertility; endometriosis.

1. INTRODUCTION

Endometriosis is characterized by the presence and growth of endometrial tissues outside of the uterine cavity [1]. The condition is a reproductive hormone-dependent inflammatory process that may occur during the menstrual cycle and result in loss of fertility and pelvic pain. The disease is progressive in nature and may exhibit symptoms ranging from moderate pain to chronic lesions outside of the pelvic cavity [1]. The epidemic of endometriosis has not been clear; however, the global prevalence was estimated for the past 30 years from diagnostic records, which showed total prevalence ranged from 15% to 71% in women [2]. The prevalence rates differ with respect to the symptoms, but the disease overall affected the wellbeing of women.

The Tejeda Equation is the proposed mechanism of action (∑(σX GnRH ⇒ JEG3f)+ (σα ^βER) ∴ NR3A1 ≥ 300-437pg/ml e (τ +30dy)∆ δEEC) for endometriosis Fig.4. It illustrates how the primary deviation in the GnRH gene, which is responsible for the production of gonadotropin-releasing hormone, an important regulator of the female reproductive system [3], contributes to the development of the disease. This deviation alters the functional effects of endometrial cells (JEG-3 or human choriocarcinoma cells), which gives signals to estrogen epithelial stroma cells (EEC), causing an elevated release of estradiol (estrogen). This is followed by the inflammation of the pelvic region with pain and intermittent spotting. Since the altered choriocarcinoma trophoblastic JEG-3 cells compromise the production of progesterone, therefore trophoblast implantation and maintenance are reduced. This results in increased rates of infertility and early miscarriage [3].

Targeted treatment options for endometriosis in patients is carried out with medical therapies or surgical interventions. However, recurrence of the disease symptoms is traditionally treated by surgery. The recurrence rate varies. However, it ranges from 6 to 67%, showing the heterogeneity of the population as stated earlier [4]. Postoperative risks of recurrence are associated with dysmenorrhea (menstrual pain) and the occurrence of pregnancy after surgery. These risks produce severe complications, and the severity of endometriosis can lead to the incidence of ovarian cancer [1,5]. Management of endometriosis and prevention of its recurrence is a challenging issue in clinical practice. Surgery is followed by risks and complications, whereas medical therapy gives suppressive effects rather than curative. In this regard, other management strategies are recommended as regimens for long-term follow up [6].

Literature is being reviewed to assist in determining the cause and effective treatments for endometriosis. The target aim is to achieve non-pharmacological pain management and symptom recovery with fewer chances of adverse events. This study, therefore, sought an integrative approach to manage the symptoms of the disease and prevent recurrence. This 3 part protocol facilitates the reversing of the mechanism of action for endometriosis at its root source. Several types of treatment modalities are included in the protocol, including nutritional improvement, exercise, stress reduction, and non-pharmacological interventions [7]. Hence, the approach devises Bis4, an integrated therapeutic plan of care that considers all human body aspects such as epigenetics, psychological health, biochemical and biophysical aspects [7]. Targeting these dynamic aspects can have a positive effect on the immune system while achieving the reversal. Study participants were given detailed instructions about their lifestyle habits, including diet, attaining, and maintaining positive energy for mind-body homeostasis and thus were monitored closely throughout the study period. Through internal, external, and

subconscious interventions, a dynamic, integrative therapy was applied.

2. RESEARCH METHODS

2.1 Primary Approach

The research is based on the primary investigation of the effect of treatment protocols given to the participants. The study was carried out for a total of 4.5 months, including a 30 days 3-day hormone panel for each participant for their hormone level test prior to and at the end of treatment administration. Rationale for the present approach is based on early evidence, which proposes the need for hormone balance and proposes the efficacy of an integrative approach. Study methods sought to address endometriosis biomarkers with integrative hormone regulation and simultaneously utilize a collective approach for disease management and prevention.

2.2 Study Setting

The study setting was designed carefully with an intention to respect the patient's dignity and choice of participating. The study was carried out in each individual participant's home, and researchers recorded the progress and outcomes with participants through telephonic and video means.

2.3 Sample and Recruitment

A total of thirty women participants aged 14-49 years were recruited into the study. Participants were required to complete informed consent and ethical approval for the study that was granted from the medical school board. Recruitment required early testing of disease diagnosis. Hence, only women with a recent diagnosis of endometriosis were included in the study. Exclusions were made for pregnant women, smokers, drug users, and other disease risks such as gynecological cancers. Participants' demographic information was recorded and preserved.

2.4 Treatment Intervention

All participants were given a 14-day Detox as part 1 of the 3 part protocol ®. It is composed of all natural organic ingredients and is a complete body cleanse. Simultaneously the provided oil was applied to the abdomen as instructed which is part 2 of the protocol. Participants were advised to take 2 capsules every other day on an empty stomach for part 1 for a total of two weeks. This was in conjunction with application of the oil from day 1 until day 90 of the protocol. For part 3, 3 capsules were ingested daily.

2.5 Other Treatment Regimes

Other regimes included the application of the oil to the abdomen and pelvic area. This was done for an hour for the entirety of the study. In addition, participants were advised to exercise with focus on the lower body, drink alkaline water and natural juices only, limitations to consumption of processed sugars, all non-GMO organic diet and no use of red meat or processed foods. Additionally, participants were required to meditate for 15 minutes daily, in the morning before beginning the routine and at night before going to bed.

2.6 Data Collection and Analysis

The study is a two-phase AB experimental design wherein the first phase, hormone measurements such as estradiol levels were recorded before administering treatment, and the second phase is collecting data after treatment intervention. Hence, after three months of treatment, participants' hormone levels were recorded, blood count was measured, and a 2-day panel was conducted to know the effects of treatments. Furthermore, participants' trans abdominal, and transvaginal imaging results were also collected for analysing remaining endometriosis. Based on this information, a descriptive approach was used for the data analysis, which produced the statistical results to be further interpreted by the researchers.

2.7 Validity and Reliability of Methods

The present methodology incorporated the factors of both validity and reliability. Varying measures were used to ensure both factors in the study. Since the treatment was provided to participants in the remote setting, therefore, researchers communicated with them by telephone regularly to maintain study validity. Similarly, reliability was ensured by including only participants with a history of endometriosis, and strategic inclusion and exclusion criteria helped to promote the study's reliability.

3. RESULTS AND ANALYSIS

The study aimed to challenge the disease Endometriosis that is prevalent in women of

reproductive age and affects a significant population size. Previously, the condition has had an uncertain mechanism of action with no suitable cure or prevention. However, through the Tejeda Equation the present integrative approach was therefore tested to assess the impact of an integrated therapy in participants suffering from the disease. *Bis4*, an immune stimulation therapeutic matrix has been presented by Dr. Tejeda is showing a direct association between biopsycho-neuro, biochemical, biophysical and epigenetic aspects. Based on the matrix model as given in Fig. 1. An integrative therapeutic approach was followed throughout the study to obtain these dynamical aspects.

Since the approach was provided in an AB experimental design, results were obtained for each kind of information achieved during data collection. Results reported the higher estradiol levels from participants before the treatment protocol. After treatment intervention, the day three hormone panel reported normal hormone levels of follicle-stimulating hormones (FSH), estradiol (estrogen), and progesterone. No traces of endometriosis were found in individuals after the treatment except for the one who had a single lesion in her left ovary, as shown in Fig. 2.

After 60-90 days post-treatment, additional information regarding participants health was recorded. Normal menstrual blood flow was reported, and a decline pre-menstrual symptoms were observed. Improvement of the symptoms included the decrease in pain during menses, no abdominal and pelvic pain, increased libido, normal bladder function, higher levels of energy, 3-5 Ibs weight loss was recorded, decreased bloating during menses period, and clarity in thinking. All these symptoms improvement showed significant immune stimulation with respected biopsycho-neuro, biochemical, biophysical and epigenetic improvement Fig. 1.

In addition, clearer results were reported with the percentage calculation for either the presence or absence of endometriosis that is shown in Fig. 3.

The present approach produced anticipated results with reflecting trends in the comprehension of data variables. Results for hormonal tests and medical imaging were reported with accuracy to assist in interpretation of the findings in the discussion.

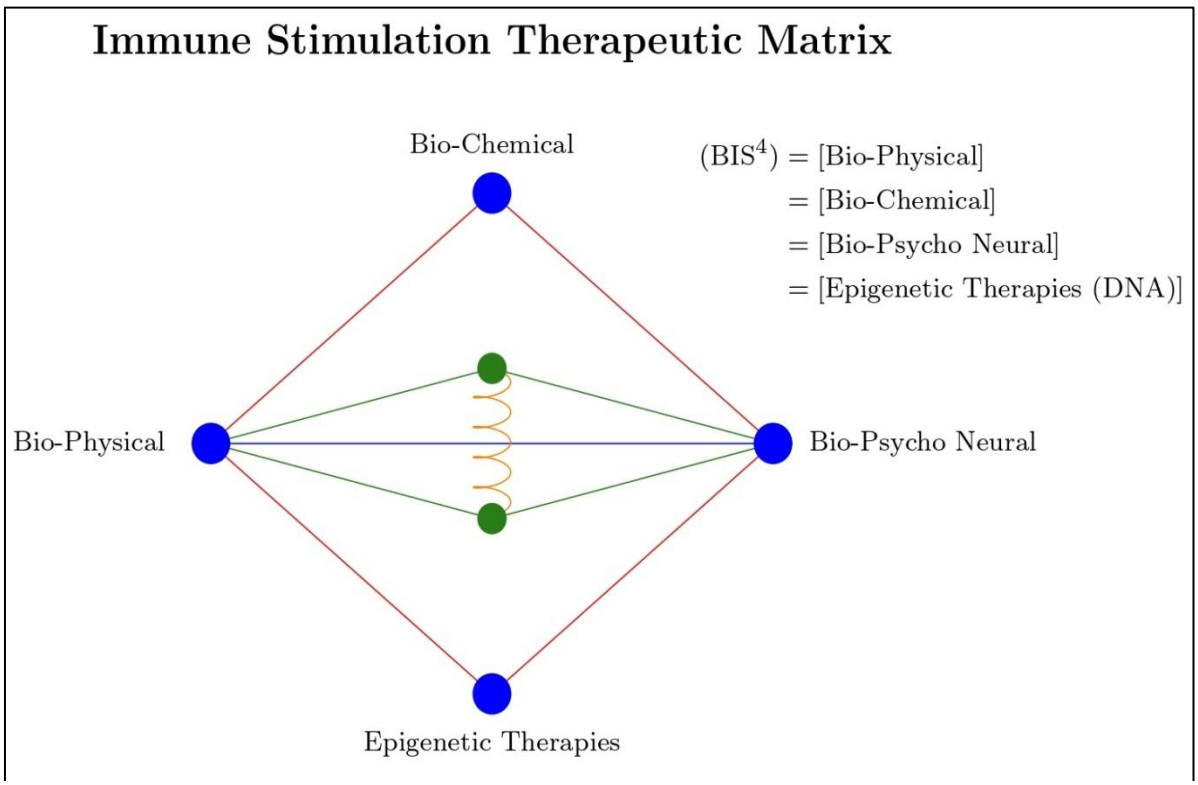

Fig. 1.

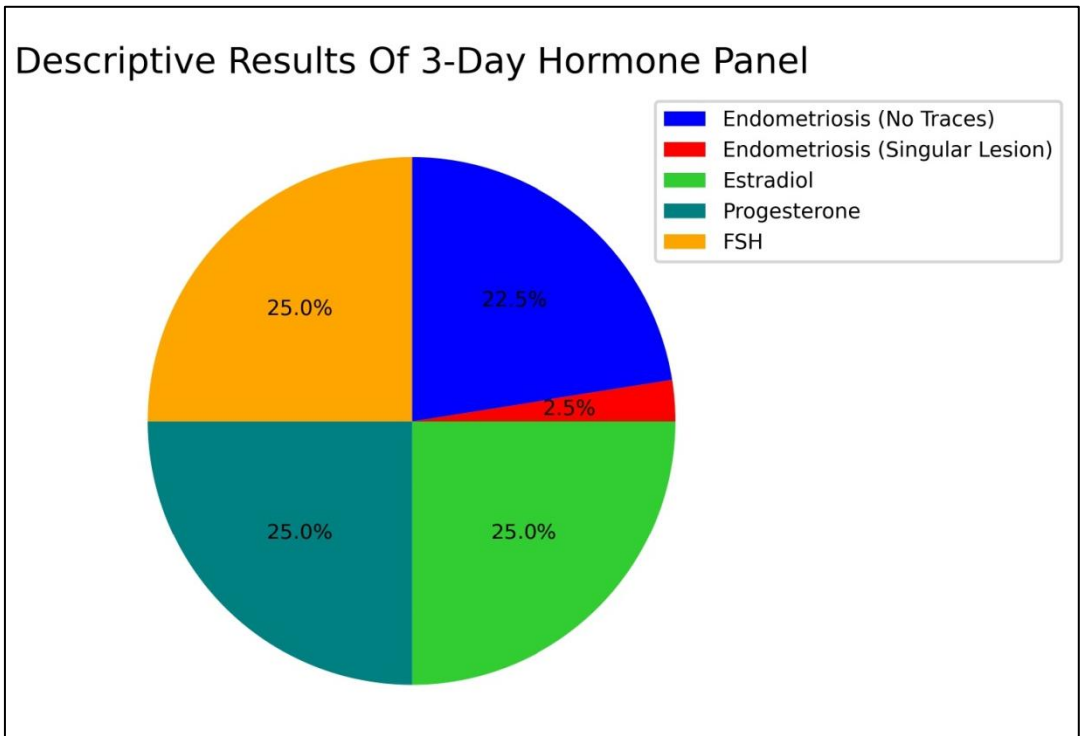
Descriptive Results Of 3-Day Hormone Panel
Endometriosis (No Traces)
Endometriosis (Singular Lesion)
Estradiol
Progesterone
FSH
25.0%
22.5%
2.5%
25.0%
25.0%

Fig. 2.

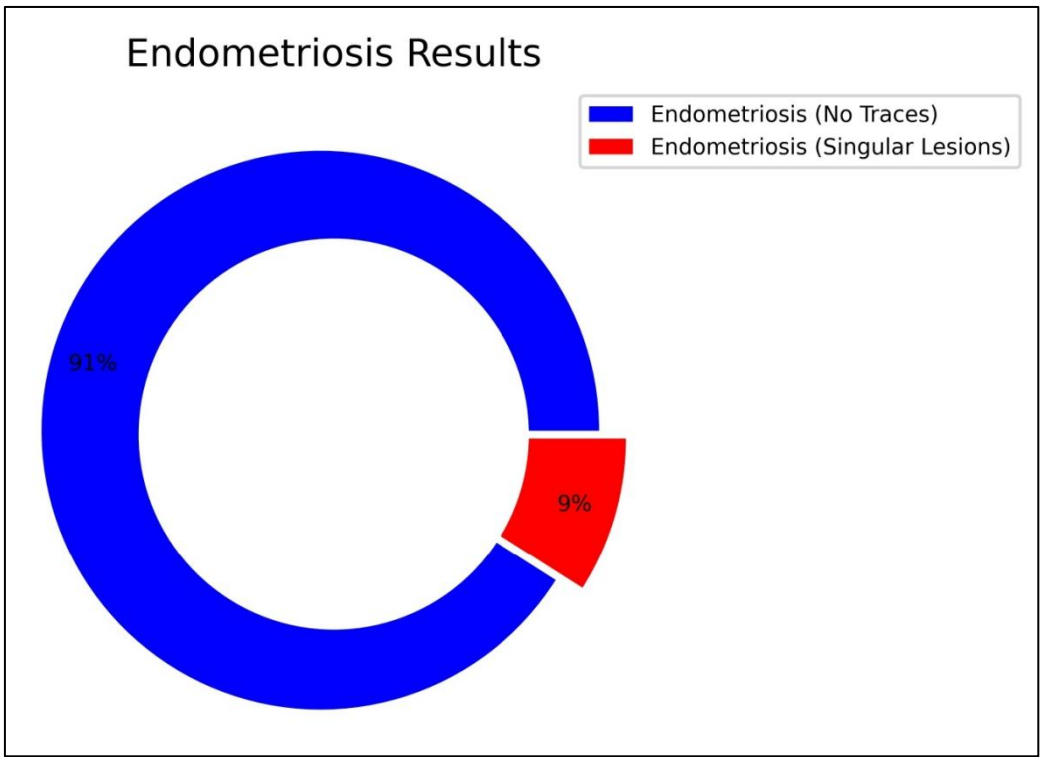
Endometriosis Results
Endometriosis (No Traces)
Endometriosis (Singular Lesions)
91%
9%

Fig. 3.

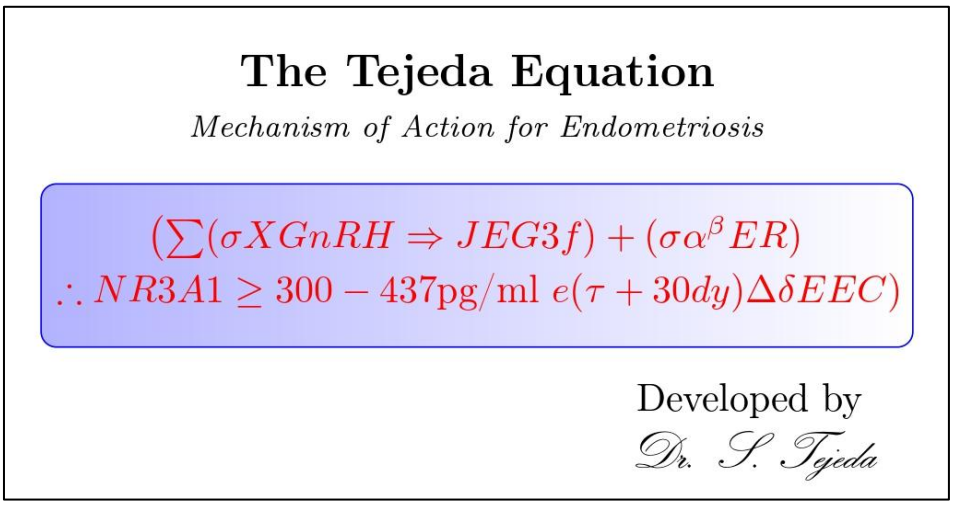

Fig. 4.

4. DISCUSSION

The study's purpose was to provide an integrated therapeutic approach to patients suffering from endometriosis. Positive health outcomes were observed for patients where the treatment intervention deactivated the mutated cell functioning. Endometriosis is a very complex disease of reproductive origin. Endometrial cells undergo a remarkable proliferation and differentiation with approximately 450 cycles in the female's reproductive lifespan [8]. However, the development of endometriosis is a multifaceted process that is caused by the combined action of different genetic, epigenetic, and environmental factors. These factors produced the effects of retrograde menstruation, metaplastic transplantation, migration, invasion, lymphatic spread, immunologic dysregulation, and inflammation. These changes are susceptible to genetic polymorphism [9]. Likewise, these disruptions cause secondary changes with the growth of lesions, angiogenesis, neurogenesis, and inflammation that are shown as the clinical manifestations.

It is imperative to understand how endometriosis is relative with sensitivity to immune actions. According to Lanišnik Rižner et al., the role of proinflammatory cytokines is quite prominent in the development of endometriosis. It was found that TNFα expression and steroidal hormones get increased during the process, which affects the isoforms of the Pak family, which regulates cellular apoptosis, motility, proliferation, and hormone-receptor signaling [10]. Pak4 also termed as P21-activated kinases, belongs to the Pak family and is responsible for endometrial cells invasion [11]. Transfection of Pak4 small-interfering RNA in endometrial cells resulted in decreased invasiveness in a knockout process. Kim et al., found a significant increase of Pak4 induced by the action of TNFα and progesterone as well [12]. Pak4 levels remain the same in the stromal cells during both proliferative and secretory phases in endometriosis patients, whereas the levels are decreased in controls subjects during the secretory phase. Pak4 immune reactivity gets increased in the eutopic endometriosis in patients. Invitro studies reported decreased Pak4 expression with progesterone treatment. This means that the progesterone-resistant phenotype causes higher Pak4 levels in endometriosis [12]. Kocbek et al., proposed that increased concentrations of IL-6 were also detected in the peritoneal fluid of women with endometriosis [13]. Similarly, IL-12 concentration is also elevated in endometriosis. Hence, immune-mediated pathophysiology is very inclusive. This mechanism accounts for endometrial cells migration and implantation to develop ectopically. This is followed by the up and down regulation of other immune cells through cell-to-cell communication with chemical signals that further leads to directing various cytokines towards the target area.

Apart from previous findings, studies have also focused on the shared alterations in ectopic lesions in women with endometriosis compared to the control, where no such alterations were observed. Kuokkanen et al., reported the up-regulation of BCL-2, an antiapoptotic protein in endometriosis, whereby increased expression enhanced the cellular proliferation and benefited the endometrium of females [14]. Therefore,

modifying the genes in cells with abnormal survival rates can impact their implantation. The genes are considered an inheritable source for migrating the pathogenic processes, which means that the close relatives of females with endometriosis are at higher risk of getting this condition compared to those who have no family history of the condition earlier [15]. Other studies found the effect of underlying genetic factors and indications for genetic modifications. Genome-wide studies revealed 30 candidate genes involved in the process, and the research is still ongoing to understand their roles. Lead researchers revealed that there is an origin of survival by endometrial cells that are discarded during the inception of endometriotic implants. Aberrant DNA hypermethylation of promoter regions of progesterone receptors is expressed in endometrial cells and direct them towards prosurvival and pro resistance to apoptosis [16]. However, since the genetic causation is still unclear and unpredictable, therefore the research is being carried out on differential gene expression during endometriosis in affected females to further identify its impact on endometrial survival.

Aside from genetic influence, the capability of endometrial cells to proliferate highly depends on the hormonal function. Kitawaki et al., proposed endometriosis as the disease showing estrogen dominance. It, therefore, became crucial to regulate the hormonal release to manage the symptoms and find the cure [17]. It was reported that high estrogen (E2) concentration because of factorial deviation releases the prostaglandin, which triggers the action of aromatase enzyme that again leads to the high production of estrogen during endometriosis [18]. Estrogen (estradiol) levels are therefore suitable targets for therapeutic interventions. The current treatment options such as dietary management or naturopathic treatments for reducing estrogen levels are promising compared to conventional hormone-based therapies with associated side effects [19]. Numerous adverse side effects included liver dysfunction, osteoporosis, bleeding, and the perimenopausal phase resulting from low estrogen levels that were induced with conventional medicines. However, the anti-endometrial effects of phytogenic medicines modulating the potential of phytoestrogen are way more beneficial to give anti-proliferative, anti-inflammatory, and anti-angiogenic responses [19]. Estrogen dependency opened a new pave for developing therapeutics to control hormonal elevation.

Apart from estrogen dependency, there is more evidence to substantiate a side view of P resistance in the pathophysiology of endometriosis. Tosti et al., reported the significant progesterone resistance (PR) in endometriotic lesions. PR expression is overall reduced relative to the eutopic endometriosis. A dysregulation of PR genes is documented in the luteal phase of the ovarian cycle [20]. In addition, progesterone effects can counteract the high E2 levels, and therefore drug developmental processes targeting the P resistance and high estrogen can abolish the endometrial lesions [20]. In addition to these changes, an important contributor is the GnRH gene response. Since endometriosis is a multifactorial disorder, therefore it is important to classify the disease for the identification of possible primary targets. It has been inclusively researched that GnRH gene mutation is primarily associated with pathophysiological responses in endometriosis [21]. It is considered a monogenic disease of mitochondrial origin which is because of its evident transfer from maternal DNA.

In the present study, the integrative treatment inclusive of its 14-day Detox, regulated the hormonal balance and reduced endometrial lesions in 90% of the cases. It is much supported by the early evidence as well. A review reported the higher recommendation of naturopathic medicines in the cases of endometriosis [22]. Similarly, women receiving naturopathic consultations were reported to have highly adhered with the healthcare services [23]. Increased nutraceutical medicines have the potential to reduce estrogen dominance alongside increasing the progesterone levels, thus facilitating the recovery from endometrial lesions that are formed because of estrogen elevation [24]. The focus of present research is to support current therapeutic approaches with complementary treatment options for such highly prevailing clinical complications in the women population. Participants in the study gave positive and anticipated outcomes, which supported the validity of our results. However, some limitations may include the general validity of the study, which is because of the minimal sample size for the research. More so, it did not evaluate the correlation with the GnRH gene. Mutation in the GnRH is a likely predictor of endometrial disruption, and therefore, clinical research also proposed the GnRH agonists as an alternative therapeutic option for the treatment of endometriotic lesions [25]. However, the potential of the present treatment protocol also

hypothesises to deactivate the mutations in GnRH genes because of its significant improvement in the symptoms and hormone levels. Furthermore, the study does not only focus on the use of naturopathic medicines but also evaluates the role of physical training and mental health balance in female patients, which shows the reliability of the treatment strategy utilizing the therapeutic model.

5. CONCLUSION

In summary, it is hypothesised that the implemented 3 part treatment protocol was successful in deactivating the mutated GnRH gene, which can restore the functional strength of JEG3 cells. However, further research is recommended in this regard, to finding more specific evidence. Ultimately, study participants were relieved of their symptoms. There was a significant reduction in endometrial lesions, and related infertility. The Endogen treatment protocol, which is researched for its GnRH agonist activity to reduce estrogen levels, should be more thoroughly investigated to ensure appropriate implications.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: Pathogenesis and treatment. Nature Reviews Endocrinology. 2014;10(5): 261-275.
2. Ghiasi M, Kulkarni MT, Missmer SA. Is endometriosis more common and more severe than it was 30 years ago? Journal of Minimally Invasive Gynecology. 2020; 27(2):452-461.
3. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertility and Sterility. 2012;98(3):511-519.
4. Bozdag G. Recurrence of endometriosis: Risk factors, mechanisms and biomarkers. Women's Health. 2015;11(5):693-699.
5. Li XY, Chao XP, Leng JH, Zhang W, Zhang JJ, Dai Y, Wu YS. Risk factors for postoperative recurrence of ovarian endometriosis: long-term follow-up of 358 women. Journal of Ovarian Research. 2019; 12(1):1-10.
6. Falcone T, Flyckt R. Clinical management of endometriosis. Obstetrics & Gynecology. 2018; 131(3):557-571.
7. Davis-Kankanamge C. The Holistic Approach to Managing Adolescent Endometriosis. In Endometriosis in Adolescents. Springer, Cham. 2020;679-684.
8. Cousins FL, Filby CE, Gargett CE. Endometrial stem/progenitor cells-their role in endometrial repair and regeneration. Frontiers in Reproductive Health. 2022;119.
9. Zubrzycka A, Zubrzycki M, Perdas E, Zubrzycka M. Genetic, epigenetic, and steroidogenic modulation mechanisms in endometriosis. Journal of Clinical Medicine. 2020;9(5):1309.
10. LanišnikRižner T. Noninvasive biomarkers of endometriosis: Myth or reality? Expert Review of Molecular Diagnostics. 2014; 14(3):365-385.
11. Lu W, Xia YH, Qu JJ. He YY, Li BL, Lu C, Wan XP. p21-activated kinase 4 regulation of endometrial cancer cell migration and invasion involves the ERK1/2 pathway mediated MMP-2 secretion. Neoplasma. 2013;060(5):493-503.
12. Kim SH, Kim SR, Ihm HJ, Oh YS, Chae HD, Kim CH, Kang BM. Regulation of P21-activated kinase-4 by progesterone and tumor necrosis factor-α in human endometrium and its increased expression in advanced-stage endometriosis. The Journal of Clinical Endocrinology & Metabolism. 2013;98(2): E238-E248.
13. Kocbek V, Vouk K, Mueller MD, Rižner TL, Bersinger NA. Elevated glycodelin-A concentrations in serum and peritoneal fluid of women with ovarian endometriosis. Gynecological Endocrinology. 2013;29(5):455-459.
14. Kuokkanen S, Chen B, Ojalvo L, Benard L, Santoro N, Pollard JW. Genomic profiling of microRNAs and messenger RNAs reveals hormonal regulation in microRNA expression in human endometrium. Biology of Reproduction. 2010;82(4):791-801.
15. Tamburro S, Canis M, Albuisson E, Dechelotte P, Darcha C, Mage G. Expression of transforming growth factor β1 in nerve fibers is related to dysmenorrhea and laparoscopic appearance of endometriotic implants. Fertility and Sterility. 2003;80(5):1131-1136.
16. Wu Y, Starzinski-Powitz A, Guo SW. Trichostatin A, a histone deacetylase inhibitor, attenuates invasiveness and

reactivates E-cadherin expression in immortalised endometriotic cells. Reproductive Sciences. 2007;14(4):374-382.

17. Kitawaki JHK. Progesterone induction of 17 -hydroxysteroid dehydrogenase type 2 during the secretory phase occurs in the BioMed Research International 13 endometrium of estrogen- dependent benign diseases but not in normal endometrium. Journal of Clinical Endocrinology and Metabolism. 2000; 3292–3296.
18. Noble LS, Takayama K, Zeitoun KM, Putman JM, Johns DA, Hinshelwood MM, Bulun SE. Prostaglandin E2 stimulates aromatase expression in endometriosis-derived stromal cells. The Journal of Clinical Endocrinology & Metabolism. 1997;82(2):600-606.
19. Gołąbek A, Kowalska K, Olejnik A. Polyphenols as a Diet Therapy Concept for Endometriosis—Current Opinion and Future Perspectives. Nutrients. 2021;13 (4):1347.
20. Tosti C, Biscione A, Morgante G, Bifulco G, Luisi S, Petraglia F. Hormonal therapy for endometriosis: from molecular research to bedside. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017; 209:61-66.
21. Dai Y, Li X, Shi J, Leng J. A review of the risk factors, genetics and treatment of endometriosis in Chinese women: a comparative update. Reproductive Health. 2018;15(1):1-12.
22. Reid R, Steel A, Wardle J, Adams J. Naturopathic medicine for the management of endometriosis, dysmenorrhea, and menorrhagia: a content analysis. The Journal of Alternative and Complementary Medicine. 2019;25(2):202-226.
23. Redmond R, Steel A, Wardle J, Adams J. Naturopathy utilisation by Australian women with diagnosed endometriosis: A cross-sectional survey. Complementary Therapies in Clinical Practice. 2022; 101539.
24. Neilson V. Integrative Endometriosis: New treatment strategies from theory to clinical application with nutraceuticals and homeopathic medicines article information. Asian Journal of Ethnopharmacology and Medicinal Food. 2018;4(2).
ISSN: 2455-4812.
25. Khan KN, Kitajima M, Hiraki K, Fujishita A, Nakashima M, Ishimaru T, Masuzaki H. Cell proliferation effect of GnRH agonist on pathological lesions of women with endometriosis, adenomyosis and uterine myoma. Human Reproduction. 2010;25 (11):2878-2890.