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PHARMACOVIGILANCE PERSPECTIVE IN ENDOMETRIOSIS: A FOCUS ON SAFETY AND THERAPEUTICS MONITORING

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ABSTRACT

The presence of endometrial-like tissue outside the uterus cavity is the hallmark of endometriosis, a chronic, estrogen-dependent gynecological illness that lowers quality of life, causes discomfort, and impairs fertility in women of reproductive age. Hormonal therapy, analgesics, and surgical procedures are used to treat endometriosis; each of these treatments has the risk of adverse drug reactions (ADRs). Pharmacovigilance, which involves ongoing monitoring, ADR identification, and reporting, is essential to guaranteeing the safe and efficient use of these treatments. The underreporting of drug-induced side effects is still a significant problem in clinical practice, even with the abundance of available treatment alternatives. In order to enhance patient safety and therapeutic results, this article emphasizes the significance of pharmacovigilance in detecting, assessing, and averting negative effects associated with medications used to treat endometriosis.

KEYWORDS: Endometriosis, Pharmacovigilance, Hormonal Therapy, Drug Monitoring, ovarian cancer in Women's Health.

INTRODUCTION

➢ What Is Endometriosis?

A medical disorder known as endometriosis occurs when tissue that resembles the lining of the uterus (known as the endometrium) begins to proliferate outside of it starts growing outside the uterus. This misplaced tissue behaves like normal uterine lining it thickens, breaks down, and bleeds during the menstrual cycle. But unlike menstrual blood, it has no way to exit the body, which leads to inflammation, pain, and sometimes scar tissue formation About 10%of women of reproductive age have endometriosis a chronic,estragon dependent condition that peaks in frequency between the ages of 25&30.The development of endometriotic lesions outside the uterus, such as in the ovaries and other pelvic tissues, is a hallmark of endometriosis.Depending upon where endometriotic lesions form, endometriosis may impact how the bladder of bowels function infertility affects up to 50% of women who have endometriosis.

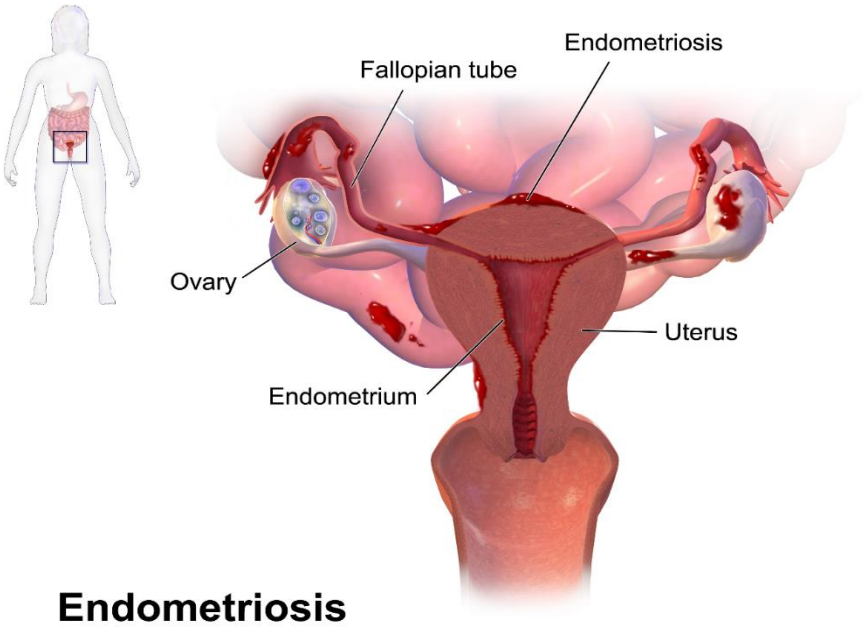

Figure 1: Endometriosis.

However, endometriosis may present with a wide range of clinical signs and symptoms, and many affected women have no signs at all There is no apparent connection between a woman's symptoms and the size of her endometriotic lesions. Based to investigations on quality of life, endometriosis symptoms impact a woman`s relationships ,social functioning, employment and education any many other areas of her life .In the USA , endometriosis is a thought to cost society more than the 49 dollars billion, with those undergoing surgery

expected to pay twice as much in direct and indirect expenses' as we all as lose productivity per woman medical Infertility dysmenorrhea, and adnexal masses are the most prevalent clinical presentation .Although the primary pathologic characteristic is the presence of ectopic endometrial tissue, endometriosis lesions differ from ectopic endometrium due to a number of molecular abnormalities because of these biological differences, creating novel medication therapy and treatments is difficult. The quality of life drops much more as symptoms deepen. Women with endometriosis reported a significant 38% decrease in work productivity in a most recent international survey, mainly due to reduced work effectiveness when pelvic pain was present one study discovered that 87% of the women with endometriosis felt depressive symptoms and 88% had anxiety, indicating that the disease impacts mental health .There was a correlation between the level of pain and the severity of anxious feelings. Families and society as a whole bear an immense financial burden from endometriosis.

➢ WHY ENDOMETRIOSIS CAUSE

Although the precise cause of endometriosis is still unknown, a number of theories have be en proposed to explain how it develops:

- **Retrograde Menstruation Theory**: Endometrial cells can implant and proliferate outside the uterus when menstrual blood flows backward through the fallopian tubes in to the pelvic cavity.
- **Coelomic Metaplasia**: In response to specific stimuli, peritoneal lining cells change into endometrial-like cells.
- **Stem cell theory** :The stem cell theory states that endometrial progenitor cell produced from bone marrow move and develop into ectopic endometrial tissue.
- **Immune Dysfunction:** Ectopic endometrial cells may be able to survive and multiply due to compromised immune surveillance.
- **Genetic Predisposition:** A heritable component may be present, as family history raises risk.

➢ COMMON SYMPTOMS OF ENDOMETRIOSIS

The severity and presentation of symptoms can vary greatly, which frequently results in a d elayed diagnosis. Among the most commonly reported are:

• Infertility: Up to 50% of women with infertility have endometriosis

• Chronic fatigue

• Gastrointestinal symptoms:- bloating, constipation, particularly during menstruation
• Urinary symptoms:- infrequently, painful urination
• Dysmenorrhea:- painful periods that may get worse over time
• Dyspareunia: -pain during sexual activity

Intense menstrual cramps, reduced back or abdominal discomfort, heavy or irregular periods, painful bowel motions or urine during menstruation, fatigue ,bloating or nausea, breast discomfort

Endometriosis related to ovarian cancer

Certain ovarian cancer subtypes, especially endometrioid and clear cell carcinomas, are more likely to occur in women with endometriosis

It has been increasingly recognised as a precursor condition for specific subtypes of ovarian cancer, particularly endometrioid and clear cell carcinoma Common molecular changes, including mutations in ARID1A, PTEN, and PIK3CA, as well as a persistently inflammatory milieu that encourages malignant development, are the causes of this connection. Because of their possible impact on carcinogenic risk, long-term hormonal treatments used to treat endometriosis, such as progestins and GnRH agonists, require close safety monitoring from a pharmacovigilance standpoint. Risk-adapted monitoring techniques, including genetic screening, MRI, transvaginal ultrasound, and **CA-125 testing**, are crucial for identifying early neoplastic alterations in individuals with chronic or atypical endometriomas. In high-risk patients, including these monitoring procedures within pharmacovigilance frameworks can increase therapeutic safety and early identification.

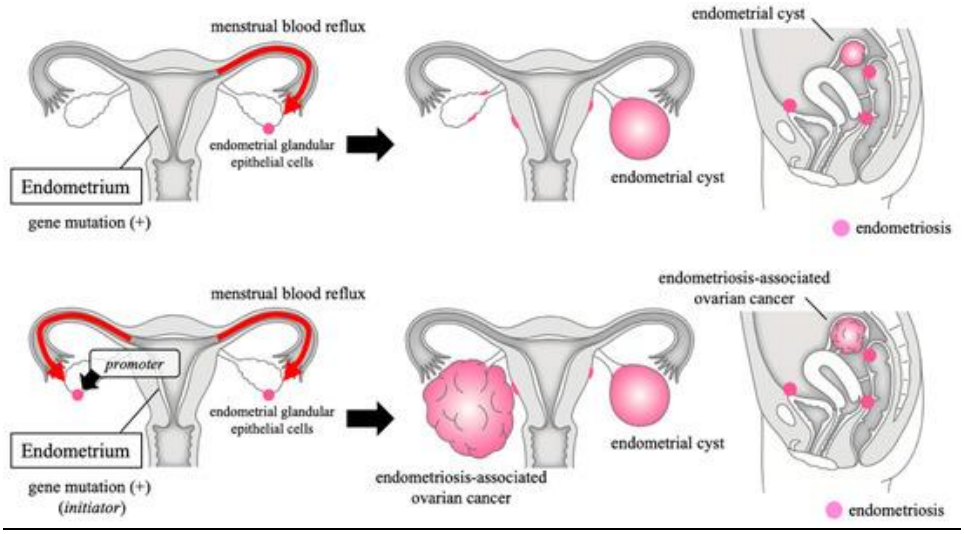

Fig. 02: Ovarian Cancer.

Emerging evidence suggests that atypical endometriosis may serve as a transitional lesion between benign endometriotic implants and malignant ovarian transformation. This underscores the importance of histopathological vigilance, especially in patients undergoing surgical excision of endometriomas. From a pharmacovigilance standpoint, the long-term safety of hormonal agents must be evaluated not only for symptom control but also for their potential role in modulating oncogenic pathways. For instance, while progestins may suppress endometrial proliferation, their impact on progesterone receptor expression in atypical lesions remains poorly understood. Additionally, the use of assisted reproductive technologies (ART) in endometriosis patients introduces another layer of complexity, as ovarian stimulation may theoretically influence neoplastic risk. Therefore, integrating pharmacovigilance with personalized risk assessment—based on lesion type, genetic markers, and treatment history—is essential for optimizing therapeutic safety and cancer prevention strategies in this vulnerable population.

CA-125

The MUC16 gene encodes the high-molecular-weight glycoprotein known as CA-125, or cancer antigen 125, which is released by Müllerian-derived epithelial cells. Because CA-125 is linked to persistent inflammation and peritoneal irritation, it has gained significance in the setting of endometriosis, despite its conventional use as a tumor marker in ovarian cancer. Serum CA-125 values, which have a generally recognized diagnostic threshold of 35 U/mL, are frequently increased in patients with moderate to severe endometriosis, especially stage III–IV. It is a helpful adjuvant in clinical evaluation because of its excellent specificity and modest sensitivity. Poorer prognostic outcomes, such as decreased overall survival and progression-free survival, have also been associated with elevated CA-125 levels, particularly when endometriosis and cancer coexist. Furthermore, immunological and hormonal variables including cortisol and estradiol, which tend to increase as the disease progresses, influence the expression of CA-125. Pharmacovigilance monitoring of CA-125 can help distinguish endometriosis from other pelvic illnesses, stratify risk for malignant transformation, and evaluate therapy response. The safety and effectiveness of long-term management techniques for gynecological illnesses are improved by its incorporation into biomarker surveillance frameworks.

Endometriosis-associated ovarian cancer (EAOC) affects fertility:-Particularly in women of reproductive age, endometriosis-associated ovarian cancer

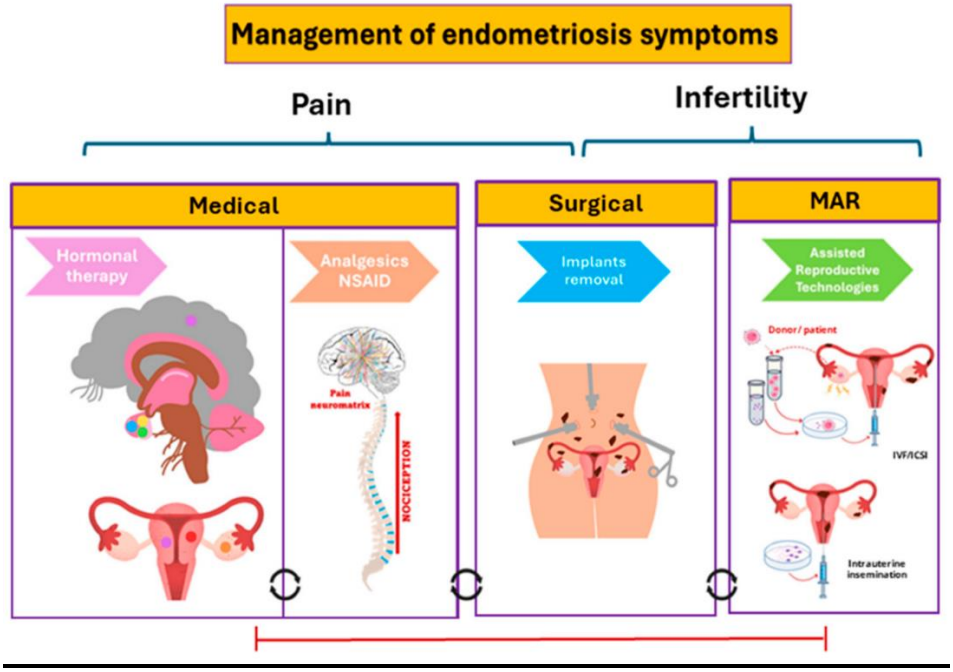

Fig. 03: Management of endometriosis symptoms.

Difficulties > (EAOC)poses special for preserving fertility. Reproductive capacity is directly compromised when endometriotic lesions malignly develop into endometrioid or clear-cell carcinomas, which frequently call for invasive surgical intervention such as oophorectomy or hysterectomy. Endometriomas and underlying inflammation can lower ovarian reserve and lower the quality of oocytes, even when fertility-sparing surgery is being considered. Furthermore, gonads toxicity after chemotherapy exposure, particularly from platinum-based regimens, can further reduce reproductive chances. Monitoring the negative effects of oncologic treatments and reproductive outcomes is crucial from the perspective of pharmacovigilance. Care plans should incorporate fertility preservation techniques, such as cryopreservation of oocytes or embryos before treatment, and longitudinal registries should be used to monitor their safety and effectiveness. This guarantees that treatment choices, especially for younger patients with EAOC, strike a balance between oncologic control and reproductive objectives.

➢ **Key ways it affects fertility**

- **Obstructed Fallopian Tubes**: If the tissue growth blocks or damages the fallopian tubes, it becomes harder for the egg and sperm to meet.
- **Ovarian Function Disruption**: Cysts known as *endometriomas* may form on the ovaries, affecting the release of healthy eggs during ovulation.

- **Inflammation and Immune Response**: The body may react to the misplaced tissue with inflammation, which can harm eggs, sperm, or embryos before implantation.
- **Scar Tissue and Adhesions**: Repeated bleeding and healing can lead to scar formation, which may distort reproductive organs and limit their movement or function.
- **Hormonal Imbalance in endometriosis**: Endometriosis can alter hormone levels, making it harder for the body to regulate ovulation and prepare the uterus for pregnancy The syndrome is characterized by estragon dominance and resistance to progesterone, which combined induce ectopic endometrial tissue growth and persistent inflammation. While poor progesterone signalling interferes with normal endometrial differentiation and immunological regulation, elevated local estragon levels, which are caused by enhanced aromatase activity in endometriotic lesions, promote proliferation and angiogenesis. In addition to discomfort and infertility, this hormone imbalance also affects how the body reacts to hormonal treatments. Monitoring the effectiveness and safety of endocrine medications, such as progestins, aromatase inhibitors, and GnRH agonists, is crucial from the standpoint of pharmacovigilance, especially in patients who have unusual disease progression or refractory symptoms. Knowing each person's unique hormonal profile may help tailor treatment and lower the possibility of side effects or treatment failure.
- **Clinical and therapeutic landscape of endometriosis :-***Disease overview and clinical impact*
- Endometriosis commonly affects people of reproductive age and causes chronic pelvic pain and reduced quality of life. Presentation and disease severity vary widely; symptom burden rather than lesion extent often guides therapy. Management objectives include pain relief, suppression of disease activity, and preservation or optimization of fertility when desired.

Therapeutic classes and clinical roles

- **Analgesics**:- Nonsteroidal anti – inflammatory drugs provide symptomatic relief but do not alter disease progression. Long term NSAID use carries well established gastrointestinal, renal, and cardiovascular risks that require routine consideration.
- **Combined hormonal contraceptives**:- Widely used for symptomatic control and cycle regulation, these agents reduce dysmenorrhea and provide contraceptive protection. Safety considerations include thromboembolism risk in predisposed individuals and metabolic effects in select patients.

- **Progestins and levonorgestrel intrauterine system (LNG IUS**): -Progestins are effective for pain suppression; LNG IUS offers localized therapy with lower systemic exposure. Common systemic effects include bleeding irregularities and mood changes.
- **Gonadotropin releasing hormone (GnRH) agonists and antagonists**:- Potent hypoestrogenic agents used for moderate to severe disease and preoperative control. Adverse effects include vasomotor symptoms, sexual dysfunction, mood alterations, and dose and duration dependent bone mineral density (BMD) loss. Add back therapy mitigates hypoestrogenic adverse effects.
- **Aromatase inhibitors and selective progesterone receptor modulators (SPRMs): -** Reserved for refractory disease or used off label in some contexts; require agent specific safety monitoring for hepatic function and endometrial effects.
- **Emerging targeted therapies and biologics**:-Under investigation; safety profiles are incompletely characterized and require post marketing pharmacovigilance when approved.

Safety profiles and adverse drug reactions

Overview of class level safety concerns:-

Analgesics (NSAIDs):-Common adverse effects include gastrointestinal discomfort, dyspepsia, and increased blood pressure. Serious events include peptic ulcer disease, gastrointestinal bleeding, renal impairment, and increased cardiovascular risk with long term use in predisposed individuals. Monitor renal function and assess gastrointestinal and cardiovascular risk when prescribing chronic NSAIDs.

Combined hormonal contraceptives:-Typical adverse effects include nausea, breast tenderness, and irregular bleeding. Serious but rare effects include venous thromboembolism, arterial thrombotic events in patients with risk factors, and rare hepatic complications. Baseline thrombotic risk assessment, counselling on smoking cessation, and monitoring of blood pressure and metabolic parameters in high- risk patients are recommended.

Progestins and levonorgestrel intrauterine system:-Common effects include irregular bleeding, amenorrhea, weight changes, and mood alterations. Serious events are uncommon but include rare thrombotic events with systemic progestins is high in risk patients and device related complications for IUS users. Monitor bleeding patterns, screen for mood disorders, and ensure device checks after insertion.

GnRH agonists and antagonists:-Hypoestrogenic side effects such as hot flashes, vaginal dryness, decreased libido, and mood swings are frequent and often dose related. Prolonged suppression leads to reductions in BMD and potential osteoporosis risk; metabolic and lipid changes may occur. Add back therapy reduces vasomotor symptoms and helps preserve bone. Monitor baseline BMD when prolonged therapy is intended and repeat at defined intervals.

Aromatase inhibitors and SPRMs:-Aromatase inhibitors can cause menopausal symptoms and musculoskeletal complaints; SPRMs can have hepatic and endometrial implications depending on the compound. Agent specific monitoring protocols should be followed for liver function tests and endometrial assessment where indicated.

Emerging agents and biologics:-Safety remains to be fully characterized. Potential concerns include immune modulation, infection risk, effects on fertility, and organ specific toxicity. Post marketing surveillance and registries are essential to capture rare and late onset events.

Treatment Approaches for Endometriosis

Endometriosis is a chronic condition, so treatment focuses **on managing symptoms, preserving fertility**, and **improving quality of life**. The choice of therapy depends on the severity of symptoms, the extent of tissue growth, and whether the individual wishes to conceive.

- **Pain Management:-Non-steroidal anti-inflammatory drugs (NSAIDs)** like ibuprofen or naproxen are often the first line of defences

- These helps to reduce menstrual cramps and pelvic pain but do not treat the underlying tissue growth.

- **Hormonal Therapies** - Hormones can slow or stop the growth of endometrial-like tissue by altering the menstrual cycle
- **Combined oral contraceptives** (estrogenic+ progestin): Regulate periods and reduce bleeding and pain
- **Progestin only options**: Pills, injections, or intrauterine devices (IUDs) that suppress menstruation.
- **GnRH agonists and antagonists**: These medications temporarily halt ovarian hormone production, inducing a reversible menopausal state to shrink endometrial lesions.
- **Aromatase inhibitors**: Used in resistant cases to block estrogenic production throughout the body.

Note: Hormonal treatments are not suitable for those actively trying to conceive.

3. Surgical Intervention: ***Surgery may be recommended when symptoms are severe or when fertility is affected***.

- **Laparoscopy**: A minimally invasive procedure to locate and remove endometrial tissue, cysts, and adhesions.
- **Laparotomy**: A more extensive surgery, rarely used unless necessary.
- **Hysterectomy**: Removal of the uterus (and sometimes ovaries), considered only when other treatments fail and childbearing is not desired.

4. **Fertility Support**:- ***For individuals facing infertility***

- **Laparoscopic surgery** may improve chances of natural conception.
- **Assisted reproductive technologies (ART)** like IVF are often recommended when anatomical damage or hormonal disruption limits natural fertility

Medications for Endometriosis & Their Adverse Effects:- Treatment aims to reduce pain, control lesion growth, and preserve fertility. Most therapies fall into two categories: **pain relief** and **hormonal regulation**.

1. Non-**Steroidal Anti-Inflammatory Drugs (NSAIDs)**: ***Used for mild to moderate pain relief***. **Examples**: Ibuprofen, Naproxen,

ADRs

- Gastric irritation or ulcers
- Nausea and vomiting
- Headache
- Kidney function impairment (with long-term use)

2. **Hormonal Contraceptives:-*Regulate menstrual cycles and reduce endometrial tissue stimulation.***

- **Examples**: Combined oral pills, vaginal rings, transdermal patches

ADRs

- Breast tenderness
- Nausea
- Mood changes
- Irregular spotting
- Increased risk of blood clots (rare but serious)

3. **Progestin Therapy:-*Suppresses ovulation and causes endometrial tissue to shrink***.

- **Examples** : Medroxyprogesterone, Norethindrone

ADRs:

- Weight gain
- Acne
- Irregular bleeding
- Depression or mood swings
- Fluid retention

4. GnRH Agonists & Antagonists:- ***Induce a temporary menopausal state to halt estrogenic production.***

- **Examples**: Leuprolide, Gosselin (agonists); Epagogic (antagonist)

ADRs

- Vaginal dryness
- Decreased libido
- Bone density loss (with prolonged use)
- Sleep disturbances

➢ **Progestin Therapy:-*Suppresses ovulation and causes endometrial tissue to shrink.***

- **Examples**: Dinenogest Medroxyprogesterone, Norethindrone

ADRs

- Weight gain
- Acne
- Irregular bleeding
- Depression or mood swings
- Fluid retention

➢ **Most Commonly Prescribed Drugs for Endometriosis**

These medications are chosen based on symptom severity, fertility goals, and individual tolerance. Here's breakdown:

Treatment with progestins: used when contraceptives containing estrogenic are inappropriate.

Forms: injectable (Depo-Provera), oral pills **(e.g., DIENOGEST 2 mg**), and intrauterine devices (IUDs) (Levonorgestrel) Its function is to shrink endometrial tissue and reduce inflammation

Dienogest 2mg in endometriosis

In dose-ranging, placebo-controlled, active comparator-controlled, and long-term trials conducted in Europe and Japan, the oral progestin dienogest2 mg has been studied systemically for the treatment of endometriosis .Dienogest2mg has been approved as a monotherapy for the treatment of endometriosis in Europe, Japan, Australia, and Singapore based on the results of this trial.

Figure 4: Dienogest 2 mg.

Dienogest 2mg and fertility considerations

Since most endometriosis patients are of reproductive age, they might need to use contraception. Dienogest2 mg offers total ovulation inhibition at a daily dosage of 2 mg, according to the data currently available.37,42,61 However, women using dienogest2mg as a treatment for endometriosis are recommended to use nonhormonal means of contraception because dienogest2mg monotherapy was not created as a contraceptive. When enough pain relief is obtained, endometriosis patients may want to become pregnant. According to recent pharmacodynamic evidence in volunteers, ovarian activity quickly returns (between 1 and 43 days) after dienogest2mg is stopped. These findings corroborate research showing a rapid recovery to fertility (mean about 30 days) and successful pregnancies in endometriosis patients after stopping dienogest2mg medication (2 mg daily) for up to a year. 52, 62, 63 There is little information available on the usage of dienogest2mg in pregnant women, just like with other progestins. The information that is currently available shows no particular

dangers during pregnancy and no detrimental effects of dienogest2mg in terms of reproductive toxicity. However, as endometriosis does not require treatment during pregnancy, dienogest2mg should not be given to expectant mothers.

> Preclinical investigation

- Dienogest 2mg has a number of characteristics in preclinical research that are crucial to its application in endometriosis.
- Pharmacologically, dienogest 2mg combines the advantageous effects of 19-norprogestin and progesteronederivative. 35, 36

Dienogest 2mg has a potent progestogenic effect after binding to the progesterone receptor with high specificity because of the high amount of the unbound molecule in the blood.

- Dienogest 2mg binds to glucocorticoid, mineralocorticoid, and estrogenic receptors with relatively low affinity Unlike other medications in the 19-norprogestin class, which do not have androgenic effects, dienogest2 mg possesses the beneficial antiandrogenic properties of progesterone derivatives, which are associated with insignificant changes in cholesterol and carbohydrate levels.38,39 Following oral administration, dienogest2mg has a high bioavailability and is almost completely absorbed, similar to other 19-norprogestins. It's extremely short 10-hour half-life means that accumulation after repeated use is not an issue.

Future Extent

Because of its complicated pathophysiology, persistent pain, and few available treatments, endometriosis remains a significant gynecological problem. Although hormonal therapy is still the mainstay of care, the possibility of negative medication interactions emphasizes how important it is to have strong pharmacovigilance systems. This review highlights the importance of data analysis, patient education, and ongoing ADR monitoring in enhancing medication safety and therapeutic results. The early identification of side effects linked to hormonal treatments can be significantly improved in the future by incorporating pharmacovigilance procedures into standard hospital processes. Monitoring can be made more effective and transparent through the use of patient-centered pharmacovigilance models, electronic health records, and digital reporting technologies. Regulatory agencies, doctors, and pharmacists working together will make drug safety networks even stronger. In order to comprehend the long-term safety profiles of existing medicines, research should also concentrate on creating safer hormonal formulations, tailored medicine strategies, and extensive real-world investigations. Future healthcare workers will be better equipped to

recognize, report, and prevent adverse drug reactions (ADRs) if awareness campaigns and pharmacovigilance training are expanded at medical and pharmacy schools. Therefore, interdisciplinary collaboration, patient involvement, and the strategic application of technology are key to the future of pharmacovigilance in the treatment of endometriosis in order to provide women with safer and more effective healthcare results.

DISCUSSION

As a complex condition, endometriosis necessitates long-term treatment with medications such progestins, oral contraceptives, gonadotropin-releasing hormone (GnRH) agonists, and nonsteroidal anti-inflammatory medicines (NSAIDs). These medications relieve symptoms, but they can have a number of negative side effects, including mood swings, weight gain, bone loss, and digestive issues. To detect these ADRs early and reduce their negative effects on patient health, ongoing pharmacovigilance is essential. Healthcare practitioners are encouraged to record and report any unexpected or severe drug responses by adverse drug reaction reporting systems like the Pharmacovigilance Programme of India (PvPI). Nonetheless, there is still a lack of knowledge on ADR reporting in endometriosis treatment among gynecologists , pharmacists, and patients. Drug safety can be greatly improved by putting risk management techniques into place and fortifying the reporting culture. Additionally, post-marketing surveillance and real-world data can offer important insights into the long-term safety profiles of hormonal and surgical treatments for endometriosis. Pharmacists are crucial to pharmacovigilance efforts because they educate patients, spot adverse drug reactions, and report results to regulatory bodies. Better adherence to therapy, safer treatment strategies, and early diagnosis of drug-related problems can result from incorporating pharmacovigilance into gyanacological practice.

CONCLUSION

In conclusion, pharmacovigilance plays a vital and indispensable role in ensuring the safe and effective management of endometriosis, particularly in patients undergoing long-term hormonal therapy. As endometriosis is a chronic and recurrent condition, the use of hormonal agents such as GnRH agonists, progestins, and oral contraceptives becomes essential, but their extended administration is often accompanied by adverse drug reactions including mood disturbances, bone mineral loss, metabolic alterations, and cardiovascular risks. These ADRs can significantly impact a patient’s quality of life and adherence to therapy if not identified and managed promptly. Therefore, hospital-based pharmacovigilance activities are crucial for

early detection, continuous monitoring, and accurate reporting of drug-related problems. Encouraging healthcare professionals—especially gynecologists, clinical pharmacists, and nurses—to actively participate in ADR reporting can strengthen the overall drug safety network. Pharmacists, in particular, play a key role by acting as a link between clinicians and patients through patient counseling**,** ADR documentation, and awareness creation. Despite the establishment of the Pharmacovigilance Programme of India (PvPI), underreporting still remains a challenge due to lack of time, awareness, and training among healthcare workers. To overcome these limitations, educational initiatives, workshops, and integration of electronic ADR reporting systems should be implemented to enhance the culture of pharmacovigilance in gynecological practice. Strengthening hospital-based monitoring and involving patients in ADR feedback mechanisms will help in generating reliable data for better regulatory decisions. Ultimately, improving pharmacovigilance in endometriosis not only ensures safer and more rational use of hormonal therapies but also contributes to enhancing women's health outcomes, patient trust, and the overall quality of healthcare delivery.

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