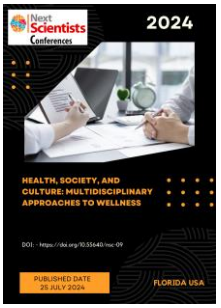
Published Date: - 25-07-2024

Page No: - 95-98



ESTETROL - A NEW APPROACH TO PRESCRIBING COCS FOR WOMEN WITH BENIGN BREAST CANCER

Aziza Lutpullaeva
Obstetrician Gynecologist Of The Republican Specialized Scientific Practical Medical Center For Maternal And Child Health Uzbekistan

ABSTRACT

Estetrol (E4), a natural estrogen synthesized exclusively by the human fetal liver during pregnancy, has garnered significant attention in recent years due to its unique properties and potential therapeutic applications. Initially discovered in 1965, E4 was largely overlooked for decades, deemed a weak estrogen with limited therapeutic potential. However, renewed interest in the early 2000s led to its development as a key component in a new combined oral contraceptive (COC). E4's prolonged half-life, high bioavailability, and low affinity for estrogen receptors make it a promising candidate for safer hormone therapy, particularly in women with benign breast cancer. Its minimal impact on liver metabolism, hemostasis, and breast health, combined with a favorable venous thromboembolism (VTE) risk profile, further supports its use in this population. This article explores the pharmacokinetics, safety profile, and therapeutic potential of estetrol, highlighting its role in a novel approach to COC prescription for women with benign breast cancer. Aziza Lutpullaeva Obstetrician Gynecologist, Republican Specialized Scientific Practical Medical Center for Maternal and Child Health, Uzbekistan

KEYWORDS: Estetrol (E4), Combined Oral Contraceptive (COC), Benign Breast Cancer, Hormone Therapy, Venous Thromboembolism (VTE), Estrogen Receptor, Pharmacokinetics, Women's Health.

INTRODUCTION

In the last few years there has been considerable interest in the estrogen, estetrol (E 4). E 4 is the estrogenic component of a recently approved combined oral contraceptive (COC) and is in development for use in menopausal hormone therapy . Based on its effects on liver metabolism, hemostasis, and breast health, as well as its favorable venous thromboembolism (VTE) risk profile, it has been suggested that E 4 has the potential to be a safer estrogen.

The natural estrogen estetrol (E4) is synthesized exclusively by the liver of the human fetus during pregnancy. E4 was discovered in 1965 at the Karolinska Institute in Stockholm and differs from estriol (E3) by an additional α-hydroxy (OH) group at position 15 of the molecule. This single additional OH group (E3) prolongs the half-life after oral administration in humans from 10-20 min for E3 to 28 h for E4. This property, together with its high bioavailability, makes E4 suitable as an oral drug.

THE MAIN RESULTS AND FINDINGS

After its discovery, research into the origin and physiological role of E 4 was conducted for the next 20+ years. After this, research into E 4 was effectively abandoned, as it was perceived as a weak estrogen with no therapeutic potential. However, in 2001, research into E 4 was revived

NEXT SCIENTISTS CONFERENCES

by Herjan Koelingh Bennink at Pantarhei Bioscience (Zeist, The Netherlands), where preclinical and clinical studies were initiated. At that time, E 4 was synthesized for industrial use at Pantarhei Bioscience using several chemical reactions starting from estrone (E 1). Renewed research led to the development of a COC containing E 4 and drospirenone. E4 binds to both the estrogen receptor (ER)-α and ER-β with low affinity compared to ethinyl estradiol and estradiol (E2) and does not bind to other steroid receptors or to a panel of 130 other drug targets. E4 is metabolized slowly in human liver cells and no active metabolites have been detected.

Unlike ethinyl estradiol and especially E2, E4 does not bind to sex hormone binding globulin (SHBG) and does not inhibit the activity of the important liver cytochrome P-450 enzymes. E4 is excreted in an inactive form by the liver and kidneys after conjugation with sulfate and/or glucuronide. Pharmacological studies have shown that E4 acts as an estrogen on the vagina, uterus and bone. E4 suppresses hot flashes in an animal model, inhibits ovulation in rats and has a vasorelaxant effect on isolated rat arteries. In animal studies with doses up to 10 mg/kg/day for 4 weeks, E4 was found to be safe and did not cause significant side effects.

Due to the emergence of E 4 as a new and very promising estrogen for therapeutic use, questions are often asked about its origin in pregnancy. Almost all recent articles on its origin claim that it is produced by the fetal liver. This claim is based on limited data showing that E 2 produced in the placenta enters the fetal compartment and is converted to E 4 in the fetal liver. Although the fetal liver plays a key role in E 4 biosynthesis, the placenta also plays an important role.

There is also data showing that E 4 is produced in the placenta from androgen precursors produced in the fetal adrenal glands and liver. In both pathways, there is interdependence between the fetus and the placenta (fetoplacental unit) in the production of E 4. Estetrol (E4) is a tissue-selective, native fetal estrogen that is currently approved for use as the estrogen component of a combined oral contraceptive and is being developed as a menopausal hormone therapy (MHT, also known as hormone replacement therapy). However, exogenous hormonal therapies, particularly MHT, have been shown to promote the growth of existing breast cancers and are associated with variable breast cancer risk depending on the treatment modality. Therefore, assessing the safety of E4-based formulations in the breast is a critical part of the clinical development process. This review highlights preclinical and clinical studies evaluating the effects of E4 and E4-progestogen combinations on breast and breast cancer, with a particular focus on the estrogenic and antiestrogenic properties of E4. Potential advantages of E4 over currently available estrogen-containing formulations as a contraceptive and for the treatment of menopausal symptoms are discussed.

Menopausal hormone therapy (MHT), also known as hormone replacement therapy (HRT), is the most powerful treatment available for relieving the symptoms associated with the cessation of estrogen production by the ovaries at menopause. However, these estrogen-based therapies are associated with an increased risk of breast cancer, and estrogens also act as growth factors in estrogen receptor-positive (ER+) breast cancers, which account for 70% of all cases. Thus, there is an unmet medical need for a new generation of MHT with an improved benefit/risk profile, particularly for breast cancer. The ideal estrogen should have the following characteristics: 1) be effective in reducing menopausal symptoms (particularly hot flashes, vulvovaginal atrophy, and osteoporosis); 2) be neutral with respect to breast growth and breast cancer; 3) neutral with respect to endometrial hyperplasia, which increases the risk of

NEXT SCIENTISTS CONFERENCES

endometrial cancer; 4) cardioprotective with respect to atherosclerosis and thromboembolism; 5) favorable metabolic profile.

This article presents the potential clinical applications of the human fetal estrogen estetrol (E 4) based on recent data from preclinical and clinical studies. In the past, E 4 was classified as a weak estrogen due to its rather low affinity for the estrogen receptor. However, recent studies have demonstrated that due to its favorable pharmacokinetic properties, especially slow elimination and long half-life, E 4 is an effective orally bioavailable estrogen agonist with antagonistic effects of estrogen on the breast in the presence of estradiol. Based on its pharmacokinetic properties, pharmacological profile and safety and efficacy results in human studies, E 4 appears to be potentially suitable as a drug for human use in areas such as hormone replacement therapy (vaginal atrophy and vasomotor symptoms), contraception, osteoporosis and breast cancer.

The safety of COCs on breast tissue has been debated in the literature over the past two decades, and overall the risk of breast cancer associated with COCs appears to remain low. However, the evidence is limited because the incidence is low, studies are complex and require very large cohorts of patients. Also of note is the small increase in risk that is observed, which disappears ten years or more after stopping treatment, highlighting that estrogens promote the growth of existing breast cancer cells rather than causing breast carcinogenesis. Furthermore, the risk of ovarian, endometrial and colorectal cancer is reduced in women using COCs and such benefits may outweigh the potential negative impact of COCs on breast cancer risk in premenopausal women. In 2002, the Women's Health Initiative (WHI) study first reported an association between MHT use and breast cancer risk. This study had unprecedented implications for MHT prescription rates, which subsequently declined by 30%. Between 2003 and 2011, several European and American epidemiological and observational studies, including the Million Women Study, the French E3N cohort, the Finnish Women Study, and the European Prospective Investigation into Cancer and Nutrition (EPIC) studies, cited breast cancer risk as the main adverse effect of MHT. In 2012, a Cochrane meta-analysis confirmed the pro-tumor risk of MHT, and in 2019, a long-term prospective study with a mean follow-up of 17.6 years showed a correlation between MHT and breast cancer-related mortality. Finally, a meta-analysis of 58 studies, including 143,887 postmenopausal women with breast cancer and 424,972 women without breast cancer, was published by the Collaborative Group on Hormonal Factors in Breast Cancer and again confirmed the correlation between MHT use and breast cancer risk. However, differences in relative risk ratios were reported by modality and all MHT formulations except oestrogen vaginal cream were associated with an increased risk.

CONCLUSION

The excess risk of breast cancer was associated with both current or recent use (1–4 years) and long-term treatment. The incidence of breast cancer was correlated with the duration of treatment and gradually decreased after treatment cessation. The association between breast cancer and MHT use was higher for estrogen–progestogen combinations compared with estrogen-only formulas or placebo. Combinations with natural progesterone and dydrogesterone appeared to be safer than those combined with synthetic progestins such as norethisterone acetate and medroxyprogesterone acetate (MPA), which increased the risk of breast cancer. Both estrogen-only and combination MHT preferentially caused ER+ breast

NEXT SCIENTISTS CONFERENCES

cancer. These observations support a role for MHT in potentiating pre-existing breast cancer cells rather than inducing carcinogenesis. It can be concluded that the risk of breast cancer in HRT users was highest when oral oestrogen-progestogen formulas were used for more than 5 years.

REFERENCES

1. Moskicheva L.I. High-intensity focused ultrasound ablation of malignant neoplasms of the mammary gland" Research in practice and in medicine 2018.
2. Mikhailovna P.A. "Optimization of diagnostics and treatment of benign pathology of the mammary glands in women of reproductive age" Abstract. Volgograd -2023.
3. Mirjam K.L., Munir Ahmed, Sarah E. Michael Duek. "Review of ablative methods for the treatment of fibroadenoma of the mammary gland" Journal of therapeutic ultrasound 01/19/2016
4. Sergeevna A.S. "The possibility of using and the effectiveness of laser radiation of the near infrared range in surgery of benign nodular neoplasms of the mammary gland". Abstract. Chelyabinsk-2012.

NEXT SCIENTISTS CONFERENCES