



Histopathological investigation of the effects of Trastuzumab on the uterus in a rat model with endometriosis

Omur Gulsum Deniz¹, Pinar Kirici², Ebru Annac³, Selcuk Kaplan⁴

¹Bolu Abant İzzet Baysal University, Faculty of Medicine, Department of Histology and Embryology, Bolu, Türkiye

²Malatya Turgut Ozal University, Faculty of Medicine, Department of Obstetrics and Gynecology, Malatya, Türkiye

³Adiyaman University, Faculty of Medicine, Department of Histology and Embryology, Adiyaman, Türkiye

⁴Adiyaman University, Faculty of Medicine, Department of Obstetrics and Gynecology, Adiyaman, Türkiye

Received 28 July 2025; Accepted 08 September 2025

Available online 27 October 2025 with doi: 10.5455/medscience.2025.07.206

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial-NonDerivatives 4.0 International License.



Abstract

It was aimed to investigate histopathological effects of trastuzumab on the uterus in a rat model with experimentally induced endometriotic tissue in the present study. In this study, 28 female Wistar albino rats (10-12 weeks old, 250-280 g) were divided into 4 groups (n =7). After a 7-day acclimation period, rats in the estrous phase were selected. The control group received no endometriosis induction; fat tissue was attached to the peritoneum and the abdomen was sutured. The endometriosis group underwent surgical induction of endometriosis using an auto-transplantation method, where uterine horn fragments were sutured to the peritoneum and mesentery. After a 4-week recovery period, the lesion size was measured, but no treatment was given. The endometriosis+Trastuzumab group received the same induction procedure as the endometriosis group, followed by intraperitoneal administration of trastuzumab (5 mg/kg) for 4 weeks. The trastuzumab group had no endometriosis induction but received the same trastuzumab dosage and schedule. Every animal tissue sample was obtained, and histopathological analysis was performed. In histopathological analysis, there was a significant difference between the Endometriosis group which had the most severe pathological changes compared to the control group (p<0.01). As well as; Endometriosis+Trastuzumab groups showed significant improvement in terms of epithelial integrity (p<0.05), Mast cell infiltration (p<0.01), glandular degeneration (p<0.05), and fibrosis (p<0.05), compared with the endometriosis group. In addition, no statistically significant difference was detected in the control and trastuzumab groups (p>0.05). Trastuzumab treatment resulted in protective effects on endometriosis-affected uterine tissue. In this context, histopathological results suggested that trastuzumab may be beneficial in treating damage caused by experimentally induced endometriosis.

Keywords: Endometriosis, trastuzumab, uterus, rat, histopathology

Introduction

The uterine lining's aberrant growth on the outside of the uterus and associated organs is a gynecological condition known as endometriosis [1] and has endometrial-like tissue outside the uterus and is a primary cause of pelvic discomfort and infertility [2]. Up to 50% of women with infertility, 50–60% of women and teenage girls experiencing chronic pelvic pain [1], and 6–10% of women of reproductive age develop endometriosis [3]. Peritoneal disease is a chronic, progressive illness that dependent on estrogen for growth, by which, endometriosis causes intrinsic Estrogen Receptor (ER)- β pathway activation

and enhanced local estradiol (E2) synthesis, which makes the ER pathway extremely active. A recent paper outlines several mechanisms that could lead to this [4]. Endometriosis is caused by retrograde menstruation of steroid hormone-sensitive endometrial cells and tissues; these cells implant on peritoneal surfaces and cause inflammation. This response is accompanied by angiogenesis, adhesions, fibrosis, scarring, neuronal infiltration, and anatomical distortion [2].

Although endometriosis has been extensively studied for many years, little is known about its etiology, and its pathophysiology is not yet fully understood [5]. However, the retrograde

CITATION

Deniz OG, Kirici P, Annac E, Kaplan S. Histopathological investigation of the effects of Trastuzumab on the uterus in a rat model with endometriosis. *Med Science*. 2025;14(4):1047-53.



Corresponding Author: Omur Gulsum Deniz, Bolu Abant İzzet Baysal University, Faculty of Medicine, Department of Histology and Embryology, Bolu, Türkiye
Email: omur.denizomu@gmail.com

menstruation/transplantation theory proposed by Sampson [6] is the most widely accepted explanation for the pathophysiology of endometriosis. This theory postulates that endometrial fragments adhere and bind to peritoneal surfaces. Sampson's theory states that a cellular blood supply and endometrial neoangiogenesis and proliferation are essential for the implantation of endometrial tissues onto peritoneal and subperitoneal surfaces [6].

Numerous malignancies in humans, such as breast, ovarian, and endometrial cancers, have been linked to human epidermal growth factor receptor 2 (HER2) gene amplification and HER2 protein overexpression which, upon ligand activation, can dimerize and trigger signal transduction via the PI3K and mitogen-activated protein kinase signaling pathways [7]. In this context, anti-HER2 treatments are now a standard of care for certain of these malignancies [7]. By binding to HER2, trastuzumab inhibits the growth, multiplication, and survival of cancer cells both directly and indirectly [8].

Current treatment limitations for endometriosis, while surgical diagnosis affords the possibility for concurrent therapy, and the removal of severe endometriosis demands specific surgical expertise. An incorrect surgical technique may result in inadequate treatment, which can lead to disease recurrence and pain, central sensitization, surgical complications, and diminished fertility [9]. In addition to that hormonal treatments that diminish endogenous estradiol levels are not an option for long-term treatment because of undesirable adverse effects, including irreversible bone mineral density (BMD), which leads to osteoporosis. [10]. Medication development is difficult when multiple requirements for the perfect endometriosis medicine are considered, including the simultaneous treatment of pain and infertility, an acceptable safety profile, safe long-term usage, and a no contraceptive impact for women of childbearing age. As a result, there is a clear need for new treatment options that target the underlying pathology of endometriosis more effectively and with fewer side effects than current hormonal or surgical treatments.

Trastuzumab is an antineoplastic biologic agent approved by the Food and Drug Administration (FDA) in the United States for medical use in the treatment of HER2-positive breast and gastric cancers in 1998, it became one of the earliest available "targeted" chemotherapies [11]. It is on the World Health Organization's List of Essential Medicines [12]. Trastuzumab may be a useful part of targeted therapy because HER2 protein overexpression or gene *erbB2* amplification is seen in 25% to 30% of serous endometrial carcinomas [11]. Trastuzumab may provide a potential treatment path worth exploring. So, we aimed to investigate histopathological effects of trastuzumab on the uterus in a rat model with experimentally induced endometriotic tissue.

Material and Methods

Animals and Experimental Protocol

Uterus tissues of the animals were used in the present study after was approved by the Adiyaman University Animal Experiments

Local Ethics Committee (no: 2022/029 dated 26/05/2022). In this research, 28 female Wistar albino rats, each weighing between 250 and 280 grams and aged 10 to 12 weeks, were divided into four groups, with each group containing seven animals. For seven days, no interventions were made to allow the caged animals for adaptation. After verifying the animals' reproductive cycles with vaginal swabs, rats in the oestrous phase were randomly selected. The following rat groups were used in the experiment:

Group 1 (Control group) (n = 7) After locating the right and left uterus horns, the abdominal wall was closed using 4-0 nylon sutures, and fat tissues were adhered to the ventral abdominal wall peritoneum without utilizing endometriotic implants [13].

Group 2 (Endometriosis group) (n = 7) In this study, endometriosis was induced using an auto-transplantation approach. Rats were given 50 mg/kg ketamine and 10 mg/kg xylazine intraperitoneally. After an abdominal incision, the right and left uterus horns were detached and cut into three to five (3-5 mm) equal portions. The small bowel mesentery and peritoneum were then inoculated with endometriotic tissue [14]. After surgically induced endometriosis, all rats were given 4 weeks to recover. After four weeks, rats underwent surgery to study the development of endometriotic implants. The endometriotic volume and implant surface areas were determined using the formula $\pi/6 \times \text{length} \times \text{width} \times \text{height}$. The peritoneal cavity was closed, the endometriotic lesions were photographed, the lesion diameters were measured, and no further treatment was administered for four weeks [13].

Group 3 (Endometriosis+Trastuzumab group) (n = 7) Similar to Group 2, endometriotic foci have been generated. Following the measurement of the endometriotic volume and the taking of pictures of the lesions, 5 mg/kg trastuzumab [13] was given intraperitoneally for 4 weeks.

Group 4 (Trastuzumab group) (n = 7) The abdominal wall was closed with 4-0 nylon stitches after the adnexa and uterus horns were identified. Trastuzumab (5 mg/kg) was injected intraperitoneally for 4 weeks, beginning simultaneously with Group 3.

Histopathological Evaluation

When the experimental application procedures were completed, uterus tissue samples belonging to the groups were taken and determined in 10% neutral-buffered formalin for 2 weeks. After the fixation process of the tissues was completed, routine histological tissue follow-up consisting of alcohol, xylene and paraplast chemicals was performed. Tissue samples were then turned into paraffin blocks. Thin sections with a thickness of 5 μm were taken from paraffin blocks for histopathological examination. The prepared sections were deparaffinized using xylene and stained with Hematoxylin-eosin, Masson's trichrome staining and Toluidine blue staining method. The stained sections were examined with a Carl Zeiss brand AxioCam ERc5 model digital camera attachment microscope and evaluated semi-quantitatively between 0 and 3. If no change occurred, the

score was 0; if mild damage was present, the score was 1; if moderate damage was evident, the score was 2; and if severe damage was observed, the score was 3.

Statistical Analysis

SPSS version 21.0 analysis program was used in the statistical analysis of the numerical data of the groups obtained from our study. The conformity of the data to the normal distribution assumption was evaluated by the Shapiro-Wilk test. In the comparison of the continuous variables specified by the measurement, the data that fit the normal distribution were evaluated using One-Way ANOVA and the Bonferroni test as post-hoc. In the statistical evaluations, the difference was accepted to be statistically significant when $p < 0.05$.

Results

Histopathological Findings of Uterus Tissue

The three layers of uterus tissue, endometrium, myometrium and perimetrium, were examined. Epithelial, glandular structures and connective tissue areas were examined in detail. It was observed that healthy tissue appearance was dominant in the control and Trastuzumab groups. It was determined that the single-layered prismatic epithelium of the endometrium and the loose connective tissue underneath were normal. Centrally located, round and oval nuclei were observed in these epithelial cells lining the lumen. The stromal cells in the connective tissue beneath the epithelial layer were located among the collagen fibers that showed a regular course (Figures 1A and B and Figures 3A and B). The blood vessels in the connective tissue appeared to maintain their structural integrity. Additionally, it was determined that the uterus gland lumens in the endometrium were clearly visible and the cells forming the gland epithelium were in a single-layered cuboidal epithelial structure (Figure 2A and B). Mast cell density in the connective tissue was found to be normal (Figure 4A and B). There were no signs of edema, fibrosis, hemorrhagic areas, or inflammation in any area in the tissue samples examined in the control and Trastuzumab groups. In the endometriosis group, degeneration and vacuolization findings were observed in the epithelium of the endometrium layer (Figure 1C). Fibrosis was observed in the connective tissue beneath the epithelium (Figure 3C). At the same time, degeneration and vacuolization were noticed in the cuboidal epithelial cells that form the structure of the endometrial glands. There was also evidence of inflammation (Figure 2C). An increase in Mast cell density in connective tissue was observed (Figure 4C). No hemorrhagic areas were found in the tissue samples examined. In the Endometriosis+Trastuzumab group, it was observed that the degenerative effects on the endometrium layer were improved. It was noticed that the structure of the single-layered prismatic epithelium surrounding its lumen was preserved (Figure 1D). A small amount of fibrosis was observed in the connective tissue under the epithelium (Figure 3D). In addition, it was determined that most of the glands in the relevant connective tissue maintained their healthy structure. In addition, there was the presence of degenerated glands. No degeneration was observed in the cubic epithelial

cells that make up its structure (Figure 2D). A decrease in mast cell density in the connective tissue was detected compared to the endometriosis group (Figure 4D). No hemorrhagic areas or any signs of inflammation were observed in the tissue samples examined.

In light of this information, a statistically significant difference ($p < 0.01$) was found between the control and endometriosis groups in terms of glandular degeneration (Figure 5A), epithelial degeneration (Figure 5B), fibrosis (Figure 5C), and Mast cell density (Figure 5D). In addition, trastuzumab was shown to significantly minimize the effects of glandular degeneration, epithelial degeneration, and fibrosis at $p < 0.05$, and Mast cell density at $p < 0.01$ level.

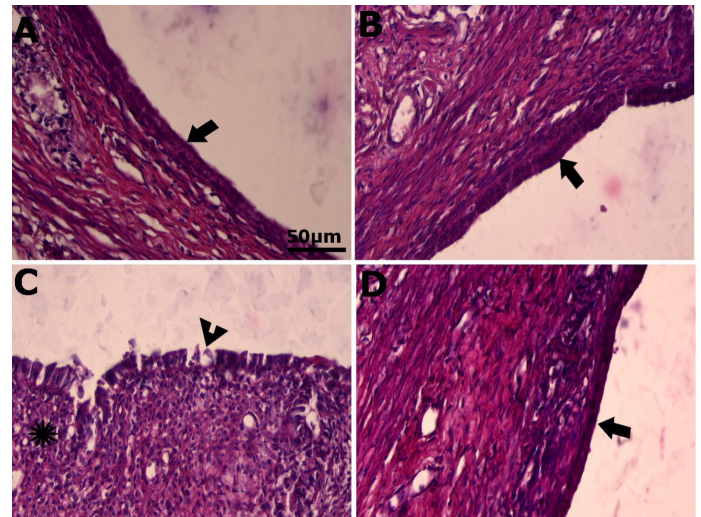


Figure 1. A, B, C, and D, histological images (Hematoxylin-eosin Staining) of the Control, Trastuzumab, Endometriosis, and Endometriosis+Trastuzumab groups at x40 objective magnification, respectively. Black arrow, prismatic epithelium with normal structure; Black arrowhead, degenerated epithelium; asterisk, inflammation.

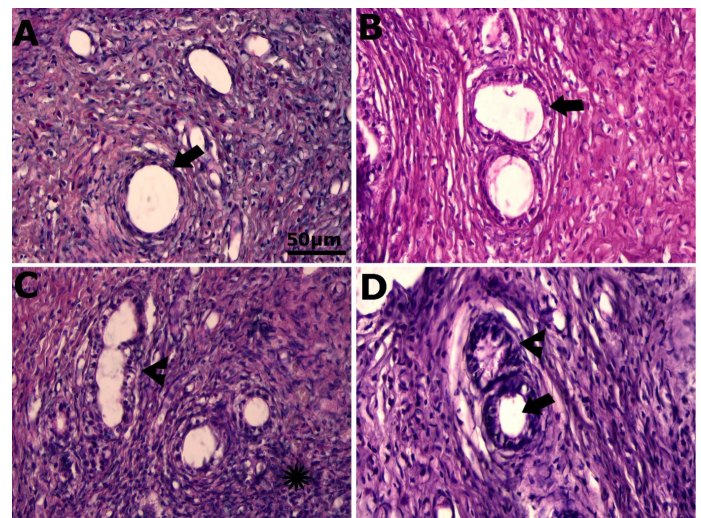


Figure 2. A, B, C, and D, Histological images (Hematoxylin-eosin Staining) of the Control, Trastuzumab, Endometriosis and Endometriosis+Trastuzumab groups at x40 objective magnification, respectively. Black arrow, gland with normal structure; Black arrowhead, degenerated gland; asterisk, inflammation.

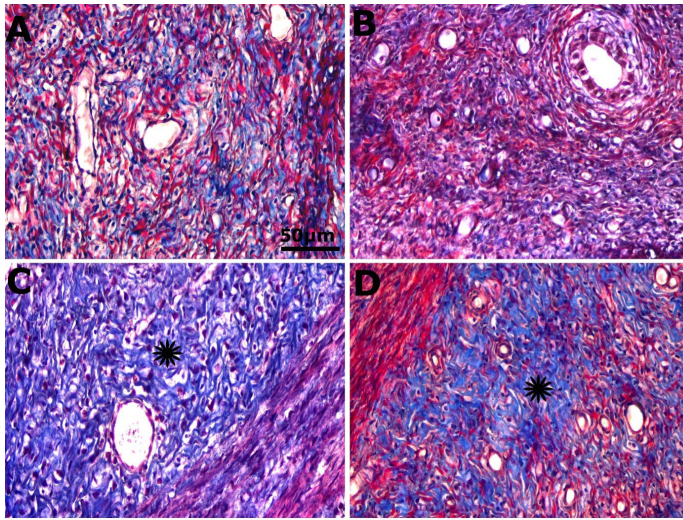


Figure 3. A, B, C, and D, Histological images (Masson's trichrome staining) of the Control, Trastuzumab, Endometriosis and Endometriosis+Trastuzumab groups at x40 objective magnification, respectively. Asterisk, fibrosis.

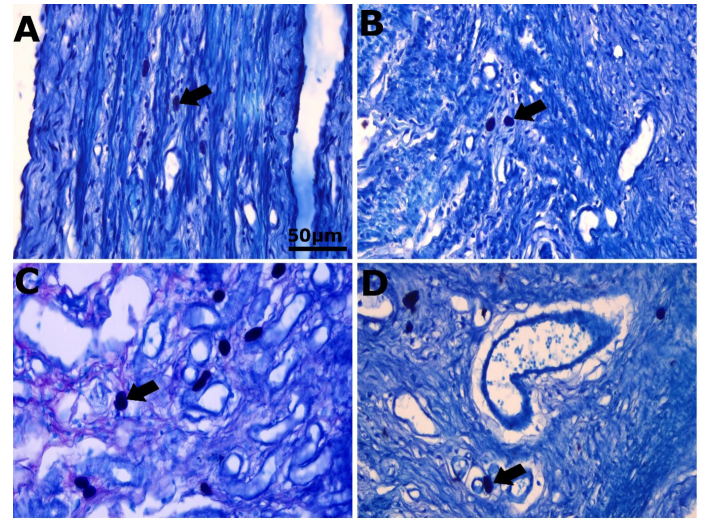


Figure 4. A, B, C, and D, Histological images (Toluidine Blue staining) of the Control, Trastuzumab, Endometriosis and Endometriosis+Trastuzumab groups at x40 objective magnification, respectively. Black arrow, Mast cell.

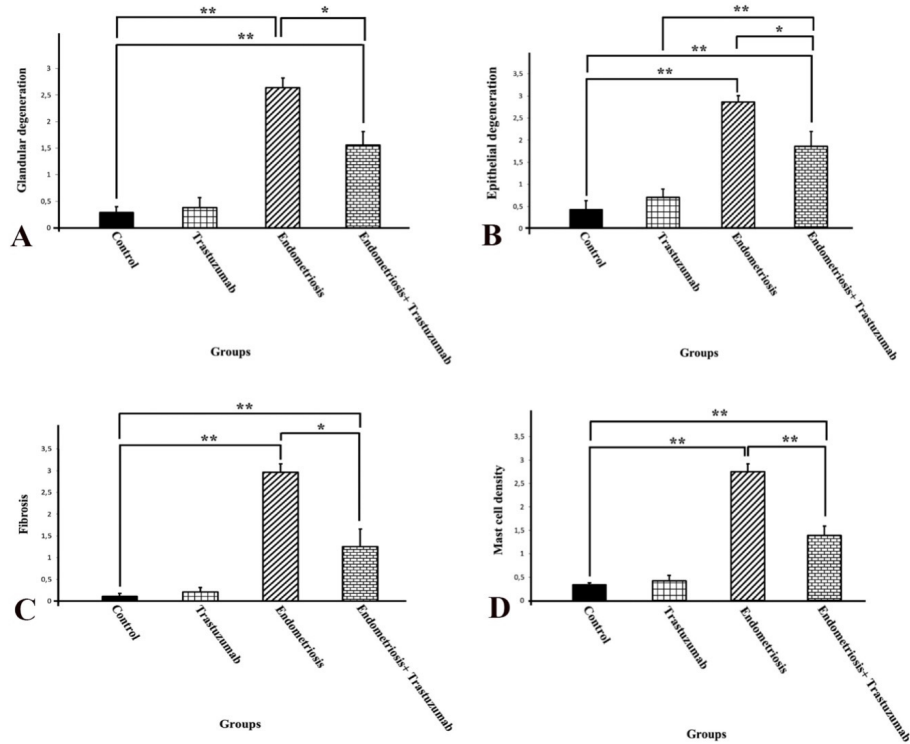


Figure 5. Glandular degeneration (A), epithelial degeneration (B), fibrosis (C) and Mast cell density (D) parameters in the uterus tissue from all groups (n=7). Differences at the p<0.05 level are indicated by “*” and those at the p<0.01 level by “**”

Discussion

Even though the first written descriptions of endometriosis were published more than a century ago, it has proven difficult to comprehend the disease's etiology and natural history [15]. There were numerous classic literatures from antiquity to the 19th century that described symptoms that were thought to be proof that endometriosis existed [16]. Nonetheless, the frequent use of rat and other models of experimental endometriosis has made it possible to identify several potentially targetable mechanisms that would otherwise contribute to the development of this illness [15]. Endometriosis is believed to be caused by an intricate combination of immunological response, neuro angiogenesis, and oxidative balance [17,18]. In a study conducted a thorough pathological examination of the rat endometriosis model. It demonstrated the presence of immune cells such as mast cells, eosinophils, plasma cells, lymphocytes, and macrophages in the peritoneal stroma surrounding implanted uterus tissue. The results indicate that the rat model closely resembles human endometriosis, making it appropriate for histopathological research [19].

Trastuzumab's histopathological effects on the uterus were examined in this work using a rat model of experimentally induced endometriotic tissue. There was significant difference between (endometriosis group) and (control and Trastuzumab groups) in terms of epithelium of the endometrium layer, that in (control and Trastuzumab groups) the single-layered prismatic epithelium of the endometrium and the loose connective tissue underneath were normal while in endometriosis group shows degeneration and vacuolization in it. Besides, in the present study, a significant difference was found between the endometriosis group and the Endometriosis+Trastuzumab group, demonstrating significant improvements in degenerative effects on the endometrial layer and a reduction in inflammation.

An investigation that induced an endometriosis model in rats to study the efficacy of natural and synthetic medications in treating endometriosis, found in the expression of the angiogenic marker vascular endothelial growth factor (VEGF), pro-inflammatory Cyclooxygenase (COX)-2 and Interleukin (IL)-6 protein markers, and anti-apoptotic Bcl-2 was significantly elevated in the endometriosis group [20] which came in support of what we obtained in our study, significant pathological alterations were consistently seen in the endometriosis group including degeneration and vacuolization, inflammation, epithelial damage, and Mast cell density.

The first anti-HER2 drug created, trastuzumab, is a humanized monoclonal antibody that attaches to the extracellular [21], ligand-binding domain [8], juxta membrane region of the HER2 receptor and inhibits HER2 signaling activity, which leads to cell cycle arrest, a decrease in angiogenesis, and an inhibition of downstream signaling pathways [8]. In our study, a decrease in histological evidence of damage in endometriotic areas in the transtuzumab-treated group was associated with the drug's

antiproliferative effect. Based on these data, it is conceivable to support the concept that endometriotic regions include HER2 receptors. Trastuzumab also reduced epithelial damage in our experiment, consistent with findings from another study where it showed improved cellular cytotoxicity over time compared to T-DM1 [22].

According to a review, fibrosis is a result of several cell types in all endometriosis symptoms. Inducing the release of substances that permit endometriosis deposit and fibrosis, fibrogenesis is facilitated by activated platelets, macrophages, ectopic endometrial cells, and sensory nerve fibers [23]. In this context, there was significant difference in our investigation between endometriosis and Endometriosis+Trastuzumab groups in terms of fibrosis. The present study demonstrated that trastuzumab treatment reduced fibrotic tissue formation in endometriosis foci. This effect may be explained by inhibition of HER2-mediated fibrogenesis signaling pathways and suppression of stromal cell activity.

Endometriosis is a chronic inflammatory illness related to estrogen. E2, a physiologically active estrogen, exacerbates the pathogenic processes such as inflammation and growth, as well as the pain symptoms associated with endometriosis [24]. Mast cells produce proteases such tryptase, which destroy extracellular matrix components and impair epithelial integrity. This action adds to the epithelial damage found in endometriotic lesions. The role of estrogen in Mast cell activity has been acknowledged as a possible contributor to the pathophysiology of various allergic and chronic inflammatory disorders. Nevertheless, detailed knowledge regarding the interaction between endocrine and immune elements in endometriotic lesions is insufficient, leaving unclear whether this interaction plays a role in the participation of Mast cells in disease pathophysiology [25]. In our study there was a significant difference between Endometriosis and Endometriosis+Trastuzumab groups in terms of Mast cell density. In this context, findings in the treatment group indicate a decrease in mast cell density, suggesting that trastuzumab may have therapeutic efficacy in reducing the pathological effects of endometriosis. Endometrial glands are tubular structures, lined with a simple columnar epithelium, located in the functional layer of the endometrium that coats the uterus [26]. The histological diagnosis of endometriosis may be complicated or obscured by an atypical appearance of the endometrial glands or the stroma, which can be influenced by inflammation, edema, or hemorrhage [27]. In our study we found a significant difference in cuboidal epithelial cells that form the structure of the endometrial glands degeneration and vacuolization were noticed in Endometriosis group while there was no degeneration observed in the cubic epithelial cells in Endometriosis+Trastuzumab group.

The use of a rat model limits the scope of this investigation, and the effectiveness of trastuzumab still requires confirmation through clinical research in humans. Although Trastuzumab's side effects most be considered which include weariness, muscle/

joint pains, discomfort, palpitations, cough and chills, and lung infiltration [28]. However, these side effects are typically moderate and do not limit its use. In addition, cardiotoxicity and interstitial pneumonia are major complications that may cause the cessation or discontinuation of treatment [29]. Furthermore, let's not underestimate that clinical studies reveal that two-thirds of patients do not respond to trastuzumab, and people who originally responded later acquire resistance to this medication [30]. On the other hand, its substantial anti-inflammatory and antiproliferative properties point to possible treatment benefits for endometriosis [13]. More research is required to better understand its mechanism and safety profile.

Conclusion

This study discovered that trastuzumab treatment resulted in significant histological improvements in endometrial structure in rats with induced endometriosis, including decreased degeneration, inflammation, and Mast cell activity. The history of endometriosis has garnered more attention throughout the last 20 years [16] use of rodent models a far more comprehensive understanding of endometriosis, by revealing its cellular pathology, early risk factors, and potential treatment targets. Vernon and Wilson [31] was one of the earliest who described the rat surgical model, despite the fact that all animal models have limitations the rat surgery model had provide important understanding of endometriosis-related peritoneal environment, inflammatory processes, the early stages of disease progression, and the function of some treatment responses and in vivo endometriosis proven effective for evaluating the therapeutic potential of natural or synthetic treatments. The best chance to find treatment approaches to stop or reverse this mysterious condition is through the ongoing development of animal models that help to understand the mechanisms behind the development of endometriosis.

The relatively short duration of the investigation constituted a limitation in terms of the long-term consequences of treatment and analysis. In this context, a longer investigation duration might be beneficial for examining oxidative balance in conjunction with the progression of chronic inflammation. Future research with additional experimental subjects is needed to support the combination and separate usage of trastuzumab in terms of long-term outcomes and adverse effects of endometriosis.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

The present study was approved by the Adiyaman University Animal Experiments Local Ethics Committee (no: 2022/029 dated 26/05/2022). All experimental procedures were carried out accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978).

References

- Butler D, Wang H, Zhang Y, et al. The effectiveness of self-supervised pre-training for multi-modal endometriosis classification. *Annu Int Conf IEEE Eng Med Biol Soc.* 2023;45:1-5.
- Giudice LC. Clinical practice. Endometriosis. *N Engl J Med.* 2010;362:2389-98.
- Yıldız Ç, Özsoy Z, Kacan T, Özer H. The effects of lapatinib and trastuzumab in a rat model of endometriosis. *Cumhuriyet Sci J.* 2022;43:556-63.
- Han SJ, Jung SY, Wu SP, et al. Estrogen receptor β modulates apoptosis complexes and the inflammasome to drive the pathogenesis of endometriosis. *Cell.* 2015;163:960-74.
- Wang Y, Nicholes K, Shih IM. The origin and pathogenesis of endometriosis. *Annu Rev Pathol.* 2020;15:71-95.
- Sampson JA. Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol.* 1927;14:422-69.
- Diver EJ, Foster R, Rueda BR, Growdon WB. The therapeutic challenge of targeting HER2 in endometrial cancer. *Oncologist.* 2015;20:1058-68.
- Boekhout AH, Beijnen JH, Schellens JHM. Trastuzumab. *Oncologist.* 2011;16:800-10.
- Pascoal E, Wessels JM, Aas-Eng MK, et al. Strengths and limitations of diagnostic tools for endometriosis and relevance in diagnostic test accuracy research. *Ultrasound Obstet Gynecol.* 2022;60:309-27.
- Zajec V, Mikuš M, Vitale SG, et al. Current status and challenges of drug development for hormonal treatment of endometriosis: a systematic review of randomized control trials. *Gynecol Endocrinol.* 2022;38:713-20.
- Findlay VJ, Scholar E. Trastuzumab. In: *xPharm: The comprehensive pharmacology reference.* StatPearls Publishing; Treasure Island, FL, USA. 2022:1-5.
- Moja L, Huttner B. Selection and use of essential medicines. In: *global health essentials.* Springer International Publishing. 2023:321-5.
- Utkan Korun ZE, Kırıcı P, Elibol E, et al. The role of toll-like receptor 4 in the development of endometriosis and the benefits of trastuzumab in the treatment of endometriosis: a rat model. *Biotech Histochem.* 2025;100:129-36.
- Pelch KE, Sharpe-Timms KL, Nagel SC. Mouse model of surgically-induced endometriosis by auto-transplantation of uterine tissue. *J Vis Exp.* 2012;59:e3396.
- Bruner-Tran KL, Mokshagundam S, Herington JL, et al. Rodent models of experimental endometriosis: identifying mechanisms of disease and therapeutic targets. *Curr Womens Heal Rev.* 2018;14:173-88.
- Benagiano G, Brosens I, Lippi D. The history of endometriosis. *Gynecol Obstet Invest.* 2014;78:1-9.
- McLaren J, Prentice A, Charnock-Jones DS, Smith SK. Vascular endothelial growth factor (VEGF) concentrations are elevated in peritoneal fluid of women with endometriosis. *Hum Reprod.* 1996;11:220-3.
- Portz DM, Elkins TE, White R, et al. Oxygen free radicals and pelvic adhesion formation: I. Blocking oxygen free radical toxicity to prevent adhesion formation in an endometriosis model. *Int J Fertil.* 1991;36:39-42.
- Uchiide I, Ihara T, Sugamata M. Pathological evaluation of the rat endometriosis model. *Fertil Steril.* 2002;78:782-6.
- Chauhan JK, Dubey PK, Rai S, Tripathi A. Induction and characterization of a rat model of endometriosis. *Sci Rep.* 2024;14:1-11.

21. Baselga J. Treatment of HER2-overexpressing breast cancer. *Ann Oncol.* 2010;21:36-40.
22. Singh H, Leyton VJ. The CL2A-SN38 linker-payload system conjugated to trastuzumab results in improved cellular cytotoxicity over time relative to T-DM1. *Mol Cancer Ther.* 2021;20:P062.
23. Viganò P, Ottolina J, Bartiromo L, et al. Cellular components contributing to fibrosis in endometriosis: A literature review. *J Minim Invasive Gynecol.* 2020;27:287-95.
24. Dyson MT, Bulun SE. Role of estrogen receptor- β in endometriosis. *Nat Med.* 2012;18:1016-8.
25. McCallion A, Nasirzadeh Y, Lingegowda H, et al. Estrogen mediates inflammatory role of mast cells in endometriosis pathophysiology. *Front Immunol.* 2022;13:961599.
26. Burton GJ, Cindrova-Davies T, Turco MY. Review: Histotrophic nutrition and the placental-endometrial dialogue during human early pregnancy Placenta. 2020;102:21-6.
27. Sahn SA, Huggins JT. Endometriosis. In: *Encyclopedia of respiratory medicine: StatPearls Publishing*, 2006:65-69.
28. Önder T, Karaçin C. Trastuzumab-induced optic neuritis: “blindness” side effect. *J Oncol Pharm Pract.* 2025;31:164-7.
29. Earl H, Hiller L, Vallier AL, et al. Six versus 12 months’ adjuvant trastuzumab in patients with HER2-positive early breast cancer: The PERSEPHONE non-inferiority RCT. *Health Technol Assess.* 2020;24:1-190.
30. Maadi H, Soheilifar MH, Choi WS, et al. Trastuzumab mechanism of action; 20 years of research to unravel a dilemma. *Cancers (Basel).* 2021;13:3540.
31. Vernon MW, Wilson EA. Studies on the surgical induction of endometriosis in the rat. *Fertil Steril.* 1985;44:684-94.