IJMS

Review Article

From Mice to Primates: Assessing Hormone-Based Endometriosis Models for Preclinical and Therapeutic Insights

Amin Tamadon[1,2], DVM, PhD; Afshin Zare[3], MD; Mahdi Mahdipour[4,5], PhD; Aria Salehpour[3], MSc; Nadiar M. Mussin[6], MD, PhD; Aliya A. Mussina[7], MD, PhD; Raisa A. Aringazina[8], MD, PhD; Ainash Duisenova[9], MD; Kulyash R. Zhilisbayeva[10], MSc; Madina A. Kurmanalina[11], MD, PhD; Chong Fu[12], MD, PhD

[1]Department of Natural Sciences, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan;
[2]Stem Cells Technology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran;
[3]PerciaVista R&D Co., Shiraz, Iran;
[4]Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran;
[5]Department of Applied Cell Sciences, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran;
[6]Department of General Surgery, West Kazakhstan Medical University, Aktobe, Kazakhstan;
[7]Department of Family Medicine No. 1, Astana Medical University, Astana, Kazakhstan;
[8]Department of Internal Medicine No. 1, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan;
[9]Department of Psychology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Republic of Kazakhstan;
[10]Department of Languages, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan;
[11]Department of Therapeutic and Prosthetic Dentistry, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan;
[12]Health Management Center, The Fifth People's Hospital of Chongqing, Chongqing, 400060, China

Correspondence:
Chong Fu, MD, PhD;
Health Management Center, The Fifth People's Hospital of Chongqing, Chongqing, 400060, China
Tel: +86 15 823258355
Email: fuxinlang66@sina.com
Received: 05 February 2025
Revised: 29 March 2025
Accepted: 18 April 2025

What's Known

- Endometriosis is a hormone-dependent gynecological disorder characterized by ectopic endometrial-like tissue growth, often studied using animal models to explore its pathogenesis and treatment.
- Previous research has established the role of sex steroid hormones and the hypothalamic-pituitary-gonadal axis in endometriosis progression, with various animal models employed to mimic the disease.

What's New

- Our comprehensive analysis highlights key improvements in model selection, emphasizing hormonal and genetic consistency with human endometriosis, thereby enhancing the reliability of preclinical studies for therapeutic development.
- This study introduces a novel scoring system to evaluate hormone-related endometriosis animal models, identifying the "unopposed estrogenicity model in baboons" as the most effective for translational research.

Abstract

Endometriosis, a complex gynecological disorder characterized by ectopic endometrial-like tissue, affects over 10% of women, causing chronic pain and infertility. Despite extensive research, its pathophysiology remains incompletely understood, with proposed mechanisms including inflammation, hormonal dysregulation, and retrograde menstruation. Given ethical and practical challenges in human studies, animal models are essential for investigating endometriosis pathogenesis and evaluating therapeutic interventions. This review examines hormone-related animal models of endometriosis, comparing induction methods (autotransplantation, xenotransplantation, and spontaneous models) and their applications in studying sex steroid hormones (SSH) and the hypothalamic-pituitary-gonadal (HPG) axis. We analyzed 158 studies (2010–2024) from PubMed Central/Medline, focusing on SSH and HPG axis involvement. A novel scoring system was developed to assess the model's suitability based on species, induction method, pharmacological effects, hormonal/genetic evaluations, histological confirmation, feasibility, ethics, and cost. Non-human primate models, particularly spontaneous and hormone-induced baboon models, scored highest due to their physiological resemblance to humans. However, rodent models remain widely used due to practicality. Our findings highlight the need for improved preclinical models to enhance translational research, ultimately aiding in the development of targeted therapies for endometriosis. This comprehensive analysis provides a framework for selecting optimal animal models in future endometriosis research.

Please cite this article as: Tamadon A, Zare A, Mahdipour M, Salehpour A, Mussin NM, Mussina AA, Aringazina RA, Duisenova A, Zhilisbayeva KR, Kurmanalina MA, Fu C. From Mice to Primates: Assessing Hormone-Based Endometriosis Models for Preclinical and Therapeutic Insights. Iran J Med Sci. doi: 10.30476/ijms.2025.105805.3975.

Keywords ● Sex steroid hormones ● Estrogens ● Progesterone ● Endometriosis ● Models, animal

Introduction

Endometriosis is a non-cancerous condition characterized by the growth of tissue resembling the endometrium in areas outside the uterine cavity. It commonly leads to symptoms such as ongoing pelvic discomfort, pain associated with the menstrual cycle, and difficulties with fertility. It is estimated that over 10% of women are affected by this condition.[1, 2] While various mechanisms of endometriosis generation have been thoroughly studied, the processes leading to its development and maintenance are not yet completely understood, and significant gaps in research remain.

The development of new surgical methods and medications for the prevention and elimination of disease or its recurrence necessitates defining the pathophysiologic mechanisms.

Endometriosis is a multifactorial disease, and various models and approaches have been proposed to explain its pathophysiology.[3] Widely accepted pathophysiological aspects can be classified as inflammation,[4] immunological factors,[5] environmental factors,[6] genetics,[7] pain,[8] infertility,[9] and hormonal. While several theories are described in each category, it is not certain which one is the primary reason for the occurrence of endometriosis. Still, one of the main theories for the ectopic formation of endometrial tissue in the peritoneal cavity is considered to be the old "retrograde menstruation".[10] Retrograde menstruation, a theory proposed over 100 years ago, suggests that menstrual blood flows backward through the fallopian tubes into the pelvic cavity.[11] While this theory has historical significance, it is important to note that more recent research has proposed alternative mechanisms for the development of endometriosis, including the stem cell origin theory.[12] This newer theory suggests that stem cells from the bone marrow or endometrial tissue itself may contribute to the formation of endometriotic lesions.[13]

Estrogen-dependency of endometriosis has been well documented,[14] and drugs that reduce or suppress sex steroid production in ovaries for endometriosis treatment[15] or relief of its symptoms, such as pain,[16] have been proposed. One of the key modulators in endometriosis pathogenesis is the increasing local production of estrogens.[17] Many effects of sex steroids are mediated by their actions at their nuclear receptors, but growing evidence suggests that some effects may occur independently of these receptors.[18] Due to the delay in diagnosing the disease and its progression by the time it is diagnosed, conducting experiments to detect predisposing factors related to synthesis or involved in sex steroid effects in endometriosis is not feasible. Due to ethical considerations, controlled experiments such as disease progression monitoring by repeated laparoscopies are limited. Therefore, animal models of endometriosis can be valuable for conducting extensive research on the effects of sex steroids and their mechanisms, including ectopic endometrial tissue adherence, invasion, and vascular establishment. They also facilitate the development of new approaches to study the initial onset, recurrence prevention, and the treatment of lesions.

The closest models to humans for evaluating endometriosis have been non-human primates. However, their use raises serious ethical concerns due to their high cognitive abilities, social structures, and the challenges associated with their care and handling. Due to their high cost and handling limitations, small laboratory animals have been used as alternative models of endometriosis. This literature review aims to provide comprehensive insight into hormone-related animal models of endometriosis and compare different induction methods, along with their advantages, disadvantages, and applications for evaluating sex steroid hormones (SSH) in the pathogenesis of endometriosis. Additionally, a summary of all published studies is provided, and a novel scoring table is designed to provide a full understanding of the most important aspects of available animal models.

We used PubMed Central/Medline databases to find research on sex hormone-related endometriosis. All included studies were published between 2010 and 2024. The Mendeley Desktop application 1.19.8 (Mendeley Ltd., London, UK) was used to screen the results. The following search query was utilized to discover all related papers, resulting in 158 related papers within our desired time interval: "endometriosis"[Title/Abstract] AND ("animal"[Title/Abstract] OR "model"[Title/Abstract]) AND ("hormone"[Title/Abstract] OR "sex"[Title/Abstract] OR "steroid"[Title/Abstract]). We included studies published between 2010 and early 2024 that proposed an endometriosis induction method in animals as the first criterion. An assessment of SSH or hypothalamic-pituitary-gonadal (HPG) axis hormones (receptors or concentration assessment) was the second inclusion criterion. We summarized all the studies that met our inclusion criteria in table 1, and articles that represented a novel induction method were classified separately. The more traditional and widely used approaches in these studies were also reviewed and explained separately.

We considered sex hormones in terms of gonadal steroid hormones: testosterone, androgens (including testosterone), estradiol, estriol, estrone (estrogens), progesterone, progestogens (including progestins) as SSH.[19] Furthermore, luteinizing hormone, follicle-stimulating hormone, gonadotropin-releasing hormone (GnRH), and melatonin were considered hormones of the HPG axis. We excluded non-English articles and review articles. We also did not consider studies that utilized steroid supplementation while inducing endometriosis in murine models as hormone-related studies.

Table 1: Hormone-based treatment of endometriosis on previously approved animal models of endometriosis.

Animal models	Author, year, Reference	Author, year, Source of utilized method
Estrogen and its receptors' role in endometriosis		
Puerarin and endometriosis	Chen et al., 2011[20]	Berkley et al., 2004[21]
Cisplatin and letrozole effect on a rat model of endometriosis	Li et al., 2016[22]	Korbel et al., 2010[23]
Telocytes damage in endometriosis-affected rat oviduct and potential impact on fertility	Yang et al., 2015[24]	Appleyard et al., 2007;[25] Vernon and Wilson, 1985[26]
Niclosamide and endometriosis	Prather et al., 2016[27]	Zhao et al., 2014[28]*
Neuroangiogenesis and endometriosis	Greaves et al., 2014[29]	Greaves et al., 2014[29]
Macrophage-nerve cross-talk and endometriosis	Greaves et al., 2015[30]	Greaves et al., 2014[29]
Simvastatin and endometriosis	Taylor et al., 2017[31]	D'Hooghe et al., 1995[32]#
Chloroindazole, oxabicycloheptene sulfonate, and endometriosis	Zhao et al., 2015[33]	Becker et al., 2006;[34] Kulak et al., 2011[35]
Progesterone family and its receptor role in endometriosis		
Levonorgestrel-loaded microspheres for the treatment of endometriosis	Yuan et al., 2012[36]	Vernon and Wilson, 1985[26]
Nomegestrol acetate and endometriosis	Zhang et al., 2014[37]	Vernon and Wilson, 1985[26]
Multi-hormone-based studies and endometriosis		
Dysregulation of steroid estrogen receptors and endometriosis	Mishra et al., 2020a[38]	Pelch et al., 2012[39]
Endometrial expression of steroidogenic factor 1 promotes cystic glandular morphogenesis.	Vasquez et al., 2016[40]	Han et al., 2012[41]*
C-Jun NH2-terminal kinase inhibitor bentamapimod and endometriosis	Palmer et al., 2016[42]	Bruner et al., 1999[43]
High-fat diet promotion of endometriosis in an immunocompetent mouse model	Heard et al., 2016[44]	Hirata et al., 2005[45]#
Extracellular matrix metalloproteinase inducer expression in the baboon endometrium: Menstrual cycle and endometriosis	Braundmeier et al., 2010[46]	D'Hooghe et al., 1995;[32] Fazleabas et al., 2002[47]
A new isoform of steroid receptor coactivator-1 is crucial for the pathogenic progression of endometriosis.	Han et al., 2012[41]	Cummings and Metcalf, 1995[48]
Krüppel-like factor 9 deficiency and endometriosis	Heard et al., 2015[49]	Hirata et al., 2005[45]#
Steroid sulfatase and endometriosis	Colette et al., 2011[50]	Defrere et al., 2006[51]
Ferulic acid, ligustrazine, and tetrahydropalmatine, and endometriosis	Tang et al., 2014[52]	Vernon and Wilson, 1985[26]
Lipoxin A4 and endometriosis	Kumar et al., 2014[53]	Vernon and Wilson, 1985[26]*
GnRH-related endometriosis		
SKI2670 and endometriosis	Kim et al., 2015[54]	Vernon and Wilson, 1985[26]
Non-GnRH hormone-related endometriosis articles		
Melatonin and endometriosis	Cetinkaya et al., 2015;[55] Koc et al., 2010;[56] Yildirim et al., 2010[57]	Guney et al., 2008;[58] Lebovic et al., 2004;[59] Uygur et al., 2006;[60] Vernon and Wilson, 1985[26]
Human chorionic gonadotropin and endometriosis	Wu et al., 2015[61]	Cotroneo and Lamartiniere, 2001[62]

#Instead of the referenced method, we mentioned the source article that provided the utilized method. *The assessed article has mentioned modification of the source method.

Hormone-Based Endometriosis Studies Utilizing Previous Induction Methods

This section includes all sex steroid hormone-related studies of endometriosis and provides comprehensive insight into assessed therapeutics for endometriosis using animal models (figure 1). Additionally, this section outlines targets of interest in the endometriosis state, mechanisms, and potential drugs that significantly ameliorate the condition. At the end of this section, a review of more frequently cited induction methods was prepared to contrast older methods with newer ones.

Hormone-based endometriosis studies have explored both the role of hormones in endometriosis treatment and their influence on the generation of endometriosis models. These studies aim to understand how hormonal fluctuations can affect the development and progression of endometriosis, as well as how hormone therapy can be used to manage its symptoms. By investigating both aspects, researchers can gain a deeper understanding of the hormonal dynamics involved in endometriosis and develop more effective therapeutic strategies. Sex steroid hormone-related studies, HPG axis hormones, and their role in endometriosis, and the frequently used methods are shown in table 1.

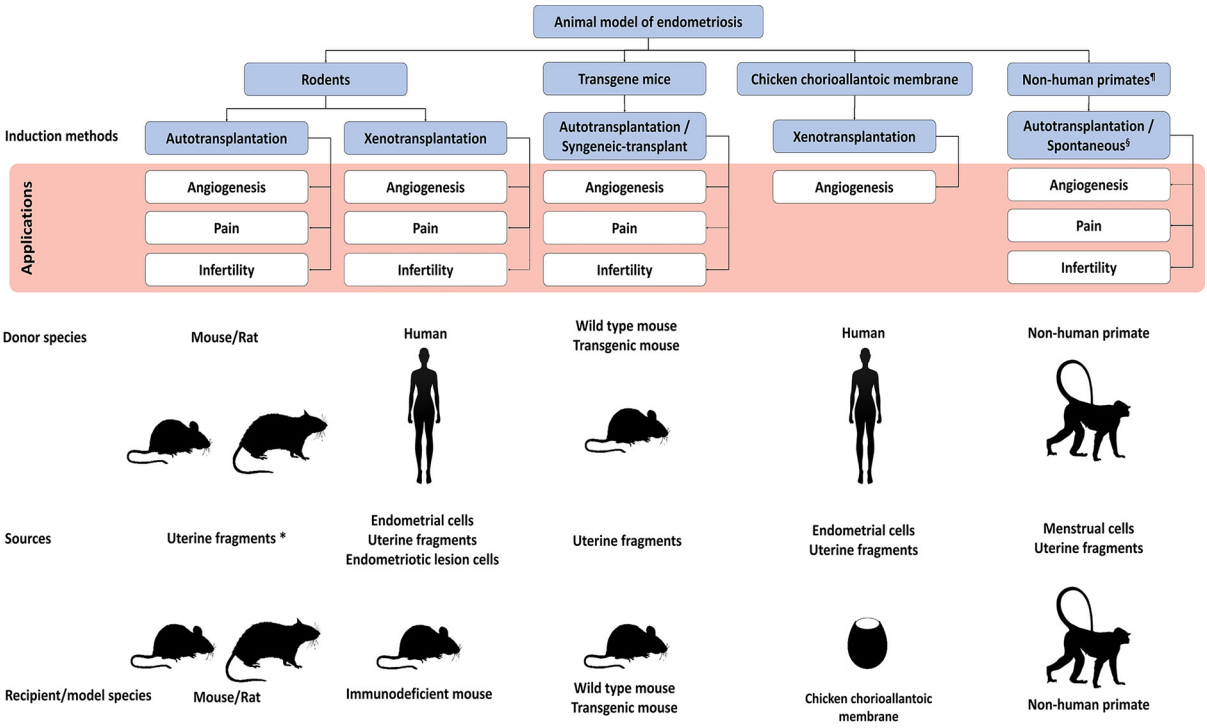

Figure 1: This figure illustrates the applications of different types of animal models in endometriosis research. ¶Non-human primate model of endometriosis is performed in species including baboons, rhesus monkeys, marmoset monkeys, and cynomolgus monkeys. §Spontaneous endometriosis is reported in baboons, rhesus monkeys, and cynomolgus monkeys

Comparison of Frequently Cited Induction Methods

The effectiveness of therapeutics in endometriosis models is influenced by the method used to induce lesions. Different methods, such as suturing, injection, gluing, and auto-transplantation, have varying effects on the inflammatory response and lesion characteristics. This section provides a comparison of these methods, highlighting their impact on study outcomes and the evaluation of treatments.

Suturing Method

Affects the inflammatory response significantly, leading to higher immune cell infiltration and more pronounced lesion development. Commonly used in studies evaluating the inflammatory pathways and immune responses to treatments.[29, 48]

Injection Method

Allows for precise control over lesion size and location, but can induce variable inflammatory responses depending on the injection site and technique.[63, 64]

Gluing Method

Provides consistent lesion induction with moderate inflammatory response, suitable for studies focusing on lesion growth and treatment efficacy.[65]

Auto-Transplantation

Mimics the natural process of endometriosis more closely, with moderate to high inflammatory response. Used in long-term studies to evaluate chronic effects and treatment outcomes.[61]

Hormone-Based Endometriosis Studies: Representing New Induction Methods

We separated studies with new approaches toward endometriosis induction to assess them exclusively with a novel scoring system. This scoring system (table 2) represents a modified combination of previously proposed scoring models to enhance the prediction of drug assessment while utilizing animal models. Detailed sections including auto-transplantation models of endometriosis related to SSH and HPG hormones, xenotransplantation models of endometriosis related to SSH and HPG hormones, allotransplantation models of endometriosis, and spontaneous endometriosis are discussed, as shown in figure 2.[75]

Scoring Table Rationale and Evaluation

We classify the induction methods into 'earlier' and 'new' categories to underscore the evolution of animal models in endometriosis research. Earlier methods, such as auto-transplantation and hormone-induced models, have been fundamental in exploring the basic mechanisms of the disease.

Table 2: Comparison of newly proposed methods of endometriosis induction for hormone-related studies

Models	Species	Induction method	Pharmacological effects	Hormonal evaluation	Genetic evaluation	Histological evaluation	Feasibility	Ethics	Financial cost	Total	Author, Year, Reference
Optimal model	2	3	1	2	2	1	1	2	0	13	-
Steroidogenic factor 1	1	1	0	0	0	1	1	1	1	6	Vasquez et al., 2016[40]
Estrogen receptor β	1	1	0	1	0	1	1	1	1	7	Han et al., 2015[66]
Activated AKT pathway	1	1	1	1	0	1	1	1	1	8	Kim et al., 2014[67]
Immortalized human eutopic endometrial stromal cells line	1	2	0	0	0	0	2	2	2	6	Huang et al., 2020[68]
Estrogen receptor signaling	1	1	0	2	1	1	1	1	1	9	Burns et al., 2012;[64] Burns et al., 2018[69]
Ovarian mouse model	1	1	0	1	1	1	2	1	2	10	Hayashi et al., 2020[70]
A high-mimicking mouse model	1	1	0	2	1	1	2	1	2	11	Greaves et al., 2014[29]
CD-1 mouse model	1	1	0	2	0	1	2	1	2	10	Kulak et al., 2011;[35] Naqvi et al., 2014[71]
Spontaneous endometriosis in a Mandrill	2	3	0	0	0	1	0	0	0	6	Nakamura et al., 2012[72]
Spontaneous endometriosis in *Rhesus Macaque*	2	3	0	0	0	1	0	0	0	6	Assaf et al., 2012[73]
Unopposed estrogenicity	2	3	1	2	0	1	1	1	1	12	Nair et al., 2016[74]

Scoring for each study is considered as follows:
Species: Non-human primate=2, Non-human mammal=1
Induction method: spontaneous disease occurrence=3, xenotransplantation=2, autotransplantation /allotransplantation=1
Pharmacological effects: Consistent drug effects with human=+1, No pharmacological evaluation=0, Non-consistent drug effects with human=-1
Hormonal evaluation: More than one similar hormonal marker regulation to human=+2, Single marker regulation similarity to human=+1, Not mentioned=0, Non-consistent hormonal marker(s) regulation(s) with human=-1
Genetic evaluation: More than one similar gene expression with human=+2, Single gene expression similarity with human=+1, No genetic evaluation=0, Non-consistent gene(s) regulation(s) with human=-1
Histological evaluation: Ectopic lesion(s) detection=+1, Not mentioned=0, No ectopic lesion(s) detection=-1
Feasibility: High feasibility=2, Moderate feasibility=1, Low feasibility=0
High feasibility (2): Models that are easy to source, maintain, and handle in most research settings (e.g., common rodents).
Moderate feasibility (1): Models that require some specialized resources or care but are still manageable (e.g., specialized rodent strains or larger mammals).
Low feasibility (0): Models that are difficult to source, require specialized environments, or are impractical for many labs (e.g., non-human primates).
Ethics: Low ethical concerns = 2, Moderate ethical concerns=1, High ethical concerns=0
Low ethical concerns (2): Models with well-established ethical guidelines and lower welfare concerns (e.g., invertebrates or lower-order mammals like mice and rats).
Moderate ethical concerns (1): Models that require more stringent oversight and ethical considerations (e.g., larger mammals).
High ethical concerns (0): Models subject to significant ethical scrutiny and regulatory requirements (e.g., non-human primates).
Financial Cost: Low cost=2, Moderate cost=1, High cost=0
Low cost (2): Models that are relatively inexpensive to acquire and maintain (e.g., common laboratory rodents).
Moderate cost (1): Models with higher acquisition or maintenance costs but still within reach for many research budgets (e.g., some specialized rodents or larger mammals).
High cost (0): Models that are very expensive to acquire, maintain, and use in research (e.g., non-human primates or very specialized animal models).

However, these methods do not fully replicate the complexities of human endometriosis, often due to oversimplification in the model design. On the other hand, new induction methods, including genetically modified animal models and more refined hormonal treatments, better reflect the natural progression of endometriosis, allowing for a more detailed exploration of its molecular and cellular mechanisms. This classification helps highlight the advancements in research methodologies and their implications for understanding the pathogenesis of endometriosis.

We used a scoring table (table 2) for model assessment, which was inspired by Ferreira and colleagues,[76] Denayer and colleagues,[77] and Sams-Dodd and others.[78] We also utilized proven hormonal markers (ER1. PR, CYP17A1) and other genetic markers (BDNF, AGTR1, CCL2, C3, CD40, TIMP2, SERPINE1, CYP17A1,

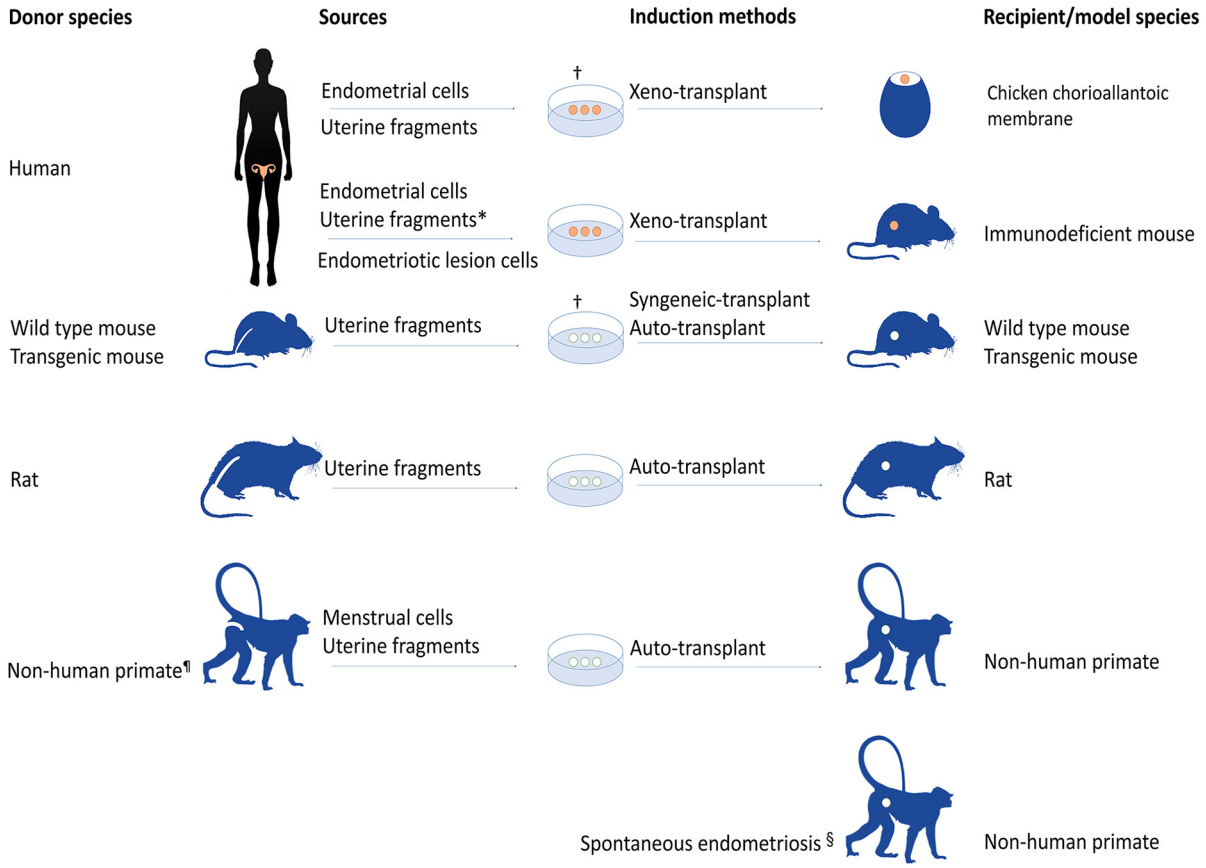

Figure 2: This figure presents different types of animal models used in endometriosis research. *Uterine tissue fragments or biopsies are used without enzymatic cell isolation. †Orange circles represent different species as the source of tissue, while white circles indicate the same species as the source of tissue. ¶The non-human primate model of endometriosis has been established in species such as baboons, rhesus monkeys, marmoset monkeys, and cynomolgus monkeys. §Spontaneous endometriosis has been reported in baboons, rhesus monkeys, and cynomolgus monkeys.

IGF1, IGF2, IL10, MMP1, MMP7, and MMP9)[79] to evaluate the models. The scoring was designed in a way that contrasts between the suitability of available studies would be easily observable.

Our scoring rationale was considered as follows:

1. Non-human primate models gained higher scores than non-human mammals due to more resemblance to humans physiologically and pathologically: (Non-human primate=2, Non-human mammal=1)

2. Spontaneous disease occurrence, which is exclusive to non-human primates, gained the highest scores. Xenotransplantation models gained higher scores than autotransplantation/ allotransplantation models due to utilizing cells or tissues from humans, which can be perceived as closer to the human pathological state:

(Spontaneous disease occurrence=3, Xenotransplantation=2, Autotransplantation / allotransplantation=1)

3. Consistent pharmacological effects in humans by available verified drugs can be a promising criterion for better future translational animal modeling:

(Consistent drug effects with human=+1, No pharmacological evaluation=0, Non-consistent drug effects with human=-1)

4. Relevant life stage in animal models is a key factor for suitability due to the occurrence of different outcomes with drug treatments in different stages of life:

(Identical life stage=+1, Not mentioned=0, Non-identical life stage=-1)

5. Previous studies have suggested extensive hormonal dysregulations in endometriotic animal models, which can comply with the human physiologic state. The more similar the dysregulation, the better the translational animal model would be:

(More than one similarity of hormonal markers regulations to human=+2, Single marker regulation similarity to human=+1, Not mentioned=0, Non-consistent hormonal marker(s) regulation(s) with human=-1)

6. Numerous genes get disrupted in the state of endometriosis. Gene regulations can be consistent with human body dysregulations or not:

(More than one similarity of genes expression

with human=+2, Single gene expression similarity with human=+1, No genetic evaluation=0, Non-consistent gene(s) regulation(s) with human=-1)

7. One of the traditional ways of validating endometriosis existence is laparoscopy. The evaluation of engaged tissues by staining or observation of ectopic lesions is still the gold standard for disease diagnosis:

(Ectopic lesion(s) detection=+1, Not mentioned=0, No ectopic lesion(s) detection=-1)

Table 2 provides novel insight for future studies to choose the most suitable model. It is worth mentioning that despite achieving fewer scores for non-human mammals than non-human primates, they benefit from wide availability, easy handling, cost-effectiveness, faster growth, and breeding. In the segment of non-human mammals, the study by Burns and colleagues,[69] Burns and coworkers,[64] and Greaves and others[29] gained the highest score by providing key elements and resemblance to human endometriosis.[29] Greaveset and others proposed their model in non-immunocompromised mice, which can be considered an advantage for studies involving immunologic topics.[29] This simple selection can produce inaccurate results for clinical trials and major analyses. Despite providing a considerable approach for xenotransplantation, Huang and colleagues did not provide an adequate animal modeling assessment.[68] Although the mouse model by Kulak and others[35] and Naqvi and colleagues[71] gained a considerable grade, it is not recommended to use the outbred stock (CD-1) due to genetic variation and the availability of other inbred mouse strains.

Transgenic animals are gaining increasing attention for further investigation in endometriosis studies. Some of these transgenic mice exhibit features of endometriosis, while others serve primarily to facilitate the investigation of the disease. The endometriotic state is induced using the previously developed methods. Transgenic animal models in this field are among the most promising tools for precisely examining the functions of various genes.

Non-human primates are considered to be very similar to humans genetically and physiologically. Additionally, they can develop spontaneous endometriosis, which can be a significant advantage for research. In addition to similarities to humans, endometriosis is confirmed more accurately considering hormonal assessment; therefore, they achieved higher scoring results. In this segment, Nair and colleagues have proposed the best model, scoring-wise.[74] Unlike other models of non-human primates, this model utilized anti-progestin to develop endometriotic lesions in baboons. Therefore, it can be proposed as the best available animal model for hormone-related endometriosis assessment.

Utilizing novel animal models to assess endometriosis pathophysiology is not a new approach.[26, 80] There has been extensive research using proposed animal models to assess etiology,[81] diagnosis,[82] resemblance,[83] genetics,[84] biomarkers,[85] and therapeutics[86] for endometriosis disease. Sometimes these studies have reported promising results in encountering endometriosis as a multifactorial gynecological disease.[87]

However, managing the challenges associated with endometriosis diagnosis remains a significant concern. Despite extensive research efforts, non-invasive, definitive, and reliable diagnostic methods for endometriosis have yet to be established.[88] Consequently, women suspected of having endometriosis still endure pain and the risks associated with invasive procedures such as laparoscopy.

Animal models have made significant contributions to understanding this disease and overcoming related challenges. However, due to limited data, comprehensive reviews such as systematic reviews or meta-analyses have struggled to fully address these issues.[89] Therefore, it is essential to revisit and revise preclinical procedures, including animal modeling, to improve research quality and generate more reliable and authentic data.

Conclusion

Endometriosis remains a complex and poorly understood gynecological disorder, necessitating reliable animal models to elucidate its pathogenesis and evaluate potential therapies. This review analyzed hormone-based animal models of endometriosis, comparing induction methods and their translational relevance. Our novel scoring system highlighted the strengths and limitations of various models, with non-human primates—particularly the unopposed estrogenicity model in baboons—emerging as the most physiologically relevant due to their close hormonal and genetic resemblance to humans. However, practical constraints such as cost, ethical considerations, and feasibility continue to make rodent models indispensable for preliminary research.

The findings underscore the need for improved preclinical models that better replicate human endometriosis, particularly in hormonal and immunological contexts. Future research should prioritize genetically modified models

and refined hormonal induction techniques to enhance translational outcomes. By optimizing model selection based on our scoring criteria, researchers can improve the reliability of preclinical studies, ultimately accelerating the development of targeted therapies for endometriosis. This comprehensive evaluation provides a valuable framework for guiding future investigations and bridging the gap between experimental findings and clinical applications.

Authors' Contribution

A.T., A.S., C.F., and M.M. conceived and designed the format of the manuscript. A.S., R.A.A., N.M.M., A.A.M., K.R.Z., M.A.K., C.F., A.D, and A.Z. collected the data and drafted and edited the manuscript. A.T., A.S., A.Z., C.F., and M.M. drew the Figures and Tables. All authors reviewed the manuscript, and all of them contributed to the critical reading and discussion of the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest: None declared.

References

1 Moradi Y, Shams-Beyranvand M, Khateri S, Gharahjeh S, Tehrani S, Varse F, et al. A systematic review on the prevalence of endometriosis in women. Indian J Med Res. 2021;154:446-54. doi: 10.4103/ijmr.IJMR_817_18. PubMed PMID: 35345070; PubMed Central PMCID: PMCPMC9131783.

2 Sarria-Santamera A, Orazumbekova B, Terzic M, Issanov A, Chaowen C, Asunsolo-Del-Barco A. Systematic Review and Meta-Analysis of Incidence and Prevalence of Endometriosis. Healthcare (Basel). 2020;9. doi: 10.3390/healthcare9010029. PubMed PMID: 33396813; PubMed Central PMCID: PMCPMC7824417.

3 Malvezzi H, Marengo EB, Podgaec S, Piccinato CA. Endometriosis: current challenges in modeling a multifactorial disease of unknown etiology. J Transl Med. 2020;18:311. doi: 10.1186/s12967-020-02471-0. PubMed PMID: 32787880; PubMed Central PMCID: PMCPMC7425005.

4 Malutan AM, Drugan T, Costin N, Ciortea R, Bucuri C, Rada MP, et al. Pro-inflammatory cytokines for evaluation of inflammatory status in endometriosis. Cent Eur J Immunol. 2015;40:96-102. doi: 10.5114/ceji.2015.50840. PubMed PMID: 26155190; PubMed Central PMCID: PMCPMC4472546.

5 Riccio L, Santulli P, Marcellin L, Abrao MS, Batteux F, Chapron C. Immunology of endometriosis. Best Pract Res Clin Obstet Gynaecol. 2018;50:39-49. doi: 10.1016/j.bpobgyn.2018.01.010. PubMed PMID: 29506962.

6 Bellelis P, Podgaec S, Abrao MS. Environmental factors and endometriosis. Rev Assoc Med Bras (1992). 2011;57:448-52. doi: 10.1590/s0104-42302011000400022. PubMed PMID: 21876930.

7 Sapkota Y, Steinthorsdottir V, Morris AP, Fassbender A, Rahmioglu N, De Vivo I, et al. Meta-analysis identifies five novel loci associated with endometriosis highlighting key genes involved in hormone metabolism. Nat Commun. 2017;8:15539. doi: 10.1038/ncomms15539. PubMed PMID: 28537267; PubMed Central PMCID: PMCPMC5458088.

8 Maddern J, Grundy L, Castro J, Brierley SM. Pain in Endometriosis. Front Cell Neurosci. 2020;14:590823. doi: 10.3389/fncel.2020.590823. PubMed PMID: 33132854; PubMed Central PMCID: PMCPMC7573391.

9 Practice Committee of the American Society for Reproductive M. Endometriosis and infertility: a committee opinion. Fertil Steril. 2012;98:591-8. doi: 10.1016/j.fertnstert.2012.05.031. PubMed PMID: 22704630.

10 Sampson JA. The development of the implantation theory for the origin of peritoneal endometriosis. American Journal of Obstetrics and Gynecology. 1940;40:549-57. doi: 10.1016/s0002-9378(40)91238-8.

11 Sampson JA. Heterotopic or misplaced endometrial tissue. American Journal of Obstetrics and Gynecology. 1925;10:649-64. doi: 10.1016/S0002-9378(25)90629-1.

12 Maruyama T. A Revised Stem Cell Theory for the Pathogenesis of Endometriosis. J Pers Med. 2022;12. doi: 10.3390/jpm12020216. PubMed PMID: 35207704; PubMed Central PMCID: PMCPMC8875896.

13 Lamceva J, Uljanovs R, Strumfa I. The Main Theories on the Pathogenesis of Endometriosis. Int J Mol Sci. 2023;24. doi: 10.3390/ijms24054254. PubMed PMID: 36901685; PubMed Central PMCID: PMCPMC10001466.

14 Bulun SE, Monsivais D, Kakinuma T, Furukawa Y, Bernardi L, Pavone ME, et al. Molecular biology of endometriosis: from aromatase to genomic abnormalities. Semin Reprod Med. 2015;33:220-4. doi: 10.1055/s-0035-1554053. PubMed PMID: 26036904.

15 Giudice LC. Clinical practice. Endometriosis. N Engl J Med. 2010;362:2389-98.

doi: 10.1056/NEJMcp1000274. PubMed PMID: 20573927; PubMed Central PMCID: PMCPMC3108065.
16 Stratton P, Berkley KJ. Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications. Hum Reprod Update. 2011;17:327-46. doi: 10.1093/humupd/dmq050. PubMed PMID: 21106492; PubMed Central PMCID: PMCPMC3072022.
17 Bulun SE, Monsavais D, Pavone ME, Dyson M, Xue Q, Attar E, et al. Role of estrogen receptor-beta in endometriosis. Semin Reprod Med. 2012;30:39-45. doi: 10.1055/s-0031-1299596. PubMed PMID: 22271293; PubMed Central PMCID: PMCPMC4034571.
18 Prossnitz ER, Barton M. The G-protein-coupled estrogen receptor GPER in health and disease. Nat Rev Endocrinol. 2011;7:715-26. doi: 10.1038/nrendo.2011.122. PubMed PMID: 21844907; PubMed Central PMCID: PMCPMC3474542.
19 Erol A, Ho AM, Winham SJ, Karpyak VM. Sex hormones in alcohol consumption: a systematic review of evidence. Addict Biol. 2019;24:157-69. doi: 10.1111/adb.12589. PubMed PMID: 29280252; PubMed Central PMCID: PMCPMC6585852.
20 Chen Y, Chen C, Shi S, Han J, Wang J, Hu J, et al. Endometriotic implants regress in rat models treated with puerarin by decreasing estradiol level. Reprod Sci. 2011;18:886-91. doi: 10.1177/1933719111398500. PubMed PMID: 21673282.
21 Berkley KJ, Dmitrieva N, Curtis KS, Papka RE. Innervation of ectopic endometrium in a rat model of endometriosis. Proc Natl Acad Sci U S A. 2004;101:11094-8. doi: 10.1073/pnas.0403663101. PubMed PMID: 15256593; PubMed Central PMCID: PMCPMC491992.
22 Li Z, Liu H, He Z, Zhang G, Lang J. Effects of cisplatin and letrozole on surgically induced endometriosis and comparison of the two medications in a rat model. Eur J Pharm Sci. 2016;93:132-40. doi: 10.1016/j.ejps.2016.07.018. PubMed PMID: 27481456.
23 Korbel C, Menger MD, Laschke MW. Size and spatial orientation of uterine tissue transplants on the peritoneum crucially determine the growth and cyst formation of endometriosis-like lesions in mice. Hum Reprod. 2010;25:2551-8. doi: 10.1093/humrep/deq201. PubMed PMID: 20693239.
24 Yang XJ, Yang J, Liu Z, Yang G, Shen ZJ. Telocytes damage in endometriosis-affected rat oviduct and potential impact on fertility. J Cell Mol Med. 2015;19:452-62. doi: 10.1111/jcmm.12427. PubMed PMID: 25388530; PubMed Central PMCID: PMCPMC4407595.
25 Appleyard CB, Cruz ML, Rivera E, Hernandez GA, Flores I. Experimental endometriosis in the rat is correlated with colonic motor function alterations but not with bacterial load. Reprod Sci. 2007;14:815-24. doi: 10.1177/1933719107309722. PubMed PMID: 18089600.
26 Vernon MW, Wilson EA. Studies on the surgical induction of endometriosis in the rat. Fertil Steril. 1985;44:684-94. PubMed PMID: 4054348.
27 Prather GR, MacLean JA, 2nd, Shi M, Boadu DK, Paquet M, Hayashi K. Niclosamide As a Potential Nonsteroidal Therapy for Endometriosis That Preserves Reproductive Function in an Experimental Mouse Model. Biol Reprod. 2016;95:76. doi: 10.1095/biolreprod.116.140236. PubMed PMID: 27535961; PubMed Central PMCID: PMCPMC5333938.
28 Zhao Y, Li Q, Katzenellenbogen BS, Lau LF, Taylor RN, Bagchi IC, et al. Estrogen-induced CCN1 is critical for establishment of endometriosis-like lesions in mice. Mol Endocrinol. 2014;28:1934-47. doi: 10.1210/me.2014-1080. PubMed PMID: 25321413; PubMed Central PMCID: PMCPMC4250364.
29 Greaves E, Cousins FL, Murray A, Esnal-Zufiaurre A, Fassbender A, Horne AW, et al. A novel mouse model of endometriosis mimics human phenotype and reveals insights into the inflammatory contribution of shed endometrium. Am J Pathol. 2014;184:1930-9. doi: 10.1016/j.ajpath.2014.03.011. PubMed PMID: 24910298; PubMed Central PMCID: PMCPMC4076466.
30 Greaves E, Temp J, Esnal-Zufiurre A, Mechsner S, Horne AW, Saunders PT. Estradiol is a critical mediator of macrophage-nerve cross talk in peritoneal endometriosis. Am J Pathol. 2015;185:2286-97. doi: 10.1016/j.ajpath.2015.04.012. PubMed PMID: 26073038; PubMed Central PMCID: PMCPMC4530129.
31 Taylor HS, Alderman Iii M, D'Hooghe TM, Fazleabas AT, Duleba AJ. Effect of simvastatin on baboon endometriosis. Biol Reprod. 2017;97:32-8. doi: 10.1093/biolre/iox058. PubMed PMID: 28637327; PubMed Central PMCID: PMCPMC6248548.
32 D'Hooghe TM, Bambra CS, Raeymaekers BM, De Jonge I, Lauweryns JM, Koninckx PR. Intrapelvic injection of menstrual endometrium causes endometriosis in baboons (Papio cynocephalus and Papio anubis). Am J Obstet Gynecol. 1995;173:125-34. doi: 10.1016/0002-9378(95)90180-9. PubMed

PMID: 7631669.
33 Zhao Y, Gong P, Chen Y, Nwachukwu JC, Srinivasan S, Ko C, et al. Dual suppression of estrogenic and inflammatory activities for targeting of endometriosis. Sci Transl Med. 2015;7:271. doi: 10.1126/scitranslmed.3010626. PubMed PMID: 25609169; PubMed Central PMCID: PMCPMC4790140.
34 Becker CM, Wright RD, Satchi-Fainaro R, Funakoshi T, Folkman J, Kung AL, et al. A novel noninvasive model of endometriosis for monitoring the efficacy of antiangiogenic therapy. Am J Pathol. 2006;168:2074-84. doi: 10.2353/ajpath.2006.051133. PubMed PMID: 16723720; PubMed Central PMCID: PMCPMC1606629.
35 Kulak J, Jr., Fischer C, Komm B, Taylor HS. Treatment with bazedoxifene, a selective estrogen receptor modulator, causes regression of endometriosis in a mouse model. Endocrinology. 2011;152:3226-32. doi: 10.1210/en.2010-1010. PubMed PMID: 21586552; PubMed Central PMCID: PMCPMC3138238.
36 Yuan P, Chen B, Huang Y, Xin X. Long-term regression of experimental endometriosis in a rat model treated with local application of levonorgestrel-loaded biodegradable microspheres. Hum Reprod. 2012;27:2089-95. doi: 10.1093/humrep/des142. PubMed PMID: 22563024.
37 Zhang J, Zhu Y, Zhou X, Hao S, Xie S, Zhou J, et al. Evaluation of biodegradable microspheres containing nomegestrol acetate in a rat model of endometriosis. Eur J Pharm Sci. 2014;65:15-20. doi: 10.1016/j.ejps.2014.08.011. PubMed PMID: 25201168.
38 Mishra A, Galvankar M, Singh N, Modi D. Spatial and temporal changes in the expression of steroid hormone receptors in mouse model of endometriosis. J Assist Reprod Genet. 2020;37:1069-81. doi: 10.1007/s10815-020-01725-6. PubMed PMID: 32152908; PubMed Central PMCID: PMCPMC7300172.
39 Pelch KE, Sharpe-Timms KL, Nagel SC. Mouse model of surgically-induced endometriosis by auto-transplantation of uterine tissue. J Vis Exp. 2012:e3396. doi: 10.3791/3396. PubMed PMID: 22257948; PubMed Central PMCID: PMCPMC3339870.
40 Vasquez YM, Wu SP, Anderson ML, Hawkins SM, Creighton CJ, Ray M, et al. Endometrial Expression of Steroidogenic Factor 1 Promotes Cystic Glandular Morphogenesis. Mol Endocrinol. 2016;30:518-32. doi: 10.1210/me.2015-1215. PubMed PMID: 27018534; PubMed Central PMCID: PMCPMC4853565.
41 Han SJ, Hawkins SM, Begum K, Jung SY, Kovanci E, Qin J, et al. A new isoform of steroid receptor coactivator-1 is crucial for pathogenic progression of endometriosis. Nat Med. 2012;18:1102-11. doi: 10.1038/nm.2826. PubMed PMID: 22660634; PubMed Central PMCID: PMCPMC3541027.
42 Palmer SS, Altan M, Denis D, Tos EG, Gotteland JP, Osteen KG, et al. Bentamapimod (JNK Inhibitor AS602801) Induces Regression of Endometriotic Lesions in Animal Models. Reprod Sci. 2016;23:11-23. doi: 10.1177/1933719115600553. PubMed PMID: 26335175; PubMed Central PMCID: PMCPMC5933194.
43 Bruner KL, Eisenberg E, Gorstein F, Osteen KG. Progesterone and transforming growth factor-beta coordinately regulate suppression of endometrial matrix metalloproteinases in a model of experimental endometriosis. Steroids. 1999;64:648-53. doi: 10.1016/s0039-128x(99)00048-3. PubMed PMID: 10503723.
44 Heard ME, Melnyk SB, Simmen FA, Yang Y, Pabona JM, Simmen RC. High-Fat Diet Promotion of Endometriosis in an Immunocompetent Mouse Model is Associated With Altered Peripheral and Ectopic Lesion Redox and Inflammatory Status. Endocrinology. 2016;157:2870-82. doi: 10.1210/en.2016-1092. PubMed PMID: 27175969; PubMed Central PMCID: PMCPMC4929556.
45 Hirata T, Osuga Y, Yoshino O, Hirota Y, Harada M, Takemura Y, et al. Development of an experimental model of endometriosis using mice that ubiquitously express green fluorescent protein. Hum Reprod. 2005;20:2092-6. doi: 10.1093/humrep/dei012. PubMed PMID: 15831509.
46 Braundmeier AG, Fazleabas AT, Nowak RA. Extracellular matrix metalloproteinase inducer expression in the baboon endometrium: menstrual cycle and endometriosis. Reproduction. 2010;140:911-20. doi: 10.1530/REP-09-0481. PubMed PMID: 20841363; PubMed Central PMCID: PMCPMC5069969.
47 Fazleabas AT, Brudney A, Gurates B, Chai D, Bulun S. A modified baboon model for endometriosis. Ann N Y Acad Sci. 2002;955:308-17; discussion 40-2, 96-406. doi: 10.1111/j.1749-6632.2002.tb02791.x. PubMed PMID: 11949957.
48 Cummings AM, Metcalf JL. Induction of endometriosis in mice: a new model sensitive to estrogen. Reprod Toxicol. 1995;9:233-8. doi: 10.1016/0890-6238(95)00004-t. PubMed PMID: 7579907.

49 Heard ME, Velarde MC, Giudice LC, Simmen FA, Simmen RC. Kruppel-Like Factor 13 Deficiency in Uterine Endometrial Cells Contributes to Defective Steroid Hormone Receptor Signaling but Not Lesion Establishment in a Mouse Model of Endometriosis. Biol Reprod. 2015;92:140. doi: 10.1095/biolreprod.115.130260. PubMed PMID: 25904015; PubMed Central PMCID: PMCPMC4652611.
50 Colette S, Defrere S, Lousse JC, Van Langendonckt A, Gotteland JP, Loumaye E, et al. Inhibition of steroid sulfatase decreases endometriosis in an in vivo murine model. Hum Reprod. 2011;26:1362-70. doi: 10.1093/humrep/der079. PubMed PMID: 21441545.
51 Defrere S, Van Langendonckt A, Gonzalez Ramos R, Jouret M, Mettlen M, Donnez J. Quantification of endometriotic lesions in a murine model by fluorimetric and morphometric analyses. Hum Reprod. 2006;21:810-7. doi: 10.1093/humrep/dei387. PubMed PMID: 16293650.
52 Tang Q, Shang F, Wang X, Yang Y, Chen G, Chen Y, et al. Combination use of ferulic acid, ligustrazine and tetrahydropalmatine inhibits the growth of ectopic endometrial tissue: a multi-target therapy for endometriosis rats. J Ethnopharmacol. 2014;151:1218-25. doi: 10.1016/j.jep.2013.12.047. PubMed PMID: 24389027.
53 Kumar R, Clerc AC, Gori I, Russell R, Pellegrini C, Govender L, et al. Lipoxin A(4) prevents the progression of de novo and established endometriosis in a mouse model by attenuating prostaglandin E(2) production and estrogen signaling. PLoS One. 2014;9:e89742. doi: 10.1371/journal.pone.0089742. PubMed PMID: 24587003; PubMed Central PMCID: PMCPMC3933674.
54 Kim SM, Yoo T, Lee SY, Kim EJ, Lee SM, Lee MH, et al. Effect of SKI2670, a novel, orally active, non-peptide GnRH antagonist, on hypothalamic-pituitary-gonadal axis. Life Sci. 2015;139:166-74. doi: 10.1016/j.lfs.2015.08.016. PubMed PMID: 26321528.
55 Cetinkaya N, Attar R, Yildirim G, Ficicioglu C, Ozkan F, Yilmaz B, et al. The effects of different doses of melatonin treatment on endometrial implants in an oophorectomized rat endometriosis model. Arch Gynecol Obstet. 2015;291:591-8. doi: 10.1007/s00404-014-3466-3. PubMed PMID: 25223860.
56 Koc O, Gunduz B, Topcuoglu A, Bugdayci G, Yilmaz F, Duran B. Effects of pinealectomy and melatonin supplementation on endometrial explants in a rat model. Eur J Obstet Gynecol Reprod Biol. 2010;153:72-6. doi: 10.1016/j.ejogrb.2010.06.012. PubMed PMID: 20667645.
57 Yildirim G, Attar R, Ozkan F, Kumbak B, Ficicioglu C, Yesildaglar N. The effects of letrozole and melatonin on surgically induced endometriosis in a rat model: a preliminary study. Fertil Steril. 2010;93:1787-92. doi: 10.1016/j.fertnstert.2009.09.021. PubMed PMID: 19878935.
58 Guney M, Oral B, Karahan N, Mungan T. Regression of endometrial explants in a rat model of endometriosis treated with melatonin. Fertil Steril. 2008;89:934-42. doi: 10.1016/j.fertnstert.2007.04.023. PubMed PMID: 17582405.
59 Lebovic DI, Kir M, Casey CL. Peroxisome proliferator-activated receptor-gamma induces regression of endometrial explants in a rat model of endometriosis. Fertil Steril. 2004;82:1008-13. doi: 10.1016/j.fertnstert.2004.02.148. PubMed PMID: 15474065.
60 Uygur D, Aytan H, Zergeroglu S, Batioglu S. Leflunomide--an immunomodulator--induces regression of endometrial explants in a rat model of endometriosis. J Soc Gynecol Investig. 2006;13:378-83. doi: 10.1016/j.jsgi.2006.03.006. PubMed PMID: 16713311.
61 Wu LL, Pang RP, Yin YZ, Shen KF, Zhang PZ. Human chorionic gonadotropin improves endometriosis through downregulation of leptin expression in rats. Gynecol Obstet Invest. 2015;79:189-94. doi: 10.1159/000367655. PubMed PMID: 25722014.
62 Cotroneo MS, Lamartiniere CA. Pharmacologic, but not dietary, genistein supports endometriosis in a rat model. Toxicol Sci. 2001;61:68-75. doi: 10.1093/toxsci/61.1.68. PubMed PMID: 11294976.
63 Dabrosin C, Gyorffy S, Margetts P, Ross C, Gauldie J. Therapeutic effect of angiostatin gene transfer in a murine model of endometriosis. Am J Pathol. 2002;161:909-18. doi: 10.1016/S0002-9440(10)64251-4. PubMed PMID: 12213719; PubMed Central PMCID: PMCPMC1867254.
64 Burns KA, Rodriguez KF, Hewitt SC, Janardhan KS, Young SL, Korach KS. Role of estrogen receptor signaling required for endometriosis-like lesion establishment in a mouse model. Endocrinology. 2012;153:3960-71. doi: 10.1210/en.2012-1294. PubMed PMID: 22700766; PubMed Central PMCID: PMCPMC3404357.
65 Boztosun A, Ozer H, Atilgan R, Acmaz G, Yalta T, Muderris, II, et al. Effect of fibrin glue and comparison with suture on experimental induction of endometriosis in a rat endometrial autograft model. Clin Exp Obstet

Gynecol. 2012;39:107-11. PubMed PMID: 22675967.
66 Han SJ, Jung SY, Wu SP, Hawkins SM, Park MJ, Kyo S, et al. Estrogen Receptor beta Modulates Apoptosis Complexes and the Inflammasome to Drive the Pathogenesis of Endometriosis. Cell. 2015;163:960-74. doi: 10.1016/j.cell.2015.10.034. PubMed PMID: 26544941; PubMed Central PMCID: PMCPMC4640214.
67 Kim TH, Yu Y, Luo L, Lydon JP, Jeong JW, Kim JJ. Activated AKT pathway promotes establishment of endometriosis. Endocrinology. 2014;155:1921-30. doi: 10.1210/en.2013-1951. PubMed PMID: 24605828; PubMed Central PMCID: PMCPMC3990849.
68 Huang ZX, Mao XM, Lin DC, Hong YH, Liang GS, Chen QX, et al. Establishment and characterization of immortalized human eutopic endometrial stromal cells. Am J Reprod Immunol. 2020;83:e13213. doi: 10.1111/aji.13213. PubMed PMID: 31802565.
69 Burns KA, Thomas SY, Hamilton KJ, Young SL, Cook DN, Korach KS. Early Endometriosis in Females Is Directed by Immune-Mediated Estrogen Receptor alpha and IL-6 Cross-Talk. Endocrinology. 2018;159:103-18. doi: 10.1210/en.2017-00562. PubMed PMID: 28927243; PubMed Central PMCID: PMCPMC5761597.
70 Hayashi S, Nakamura T, Motooka Y, Ito F, Jiang L, Akatsuka S, et al. Novel ovarian endometriosis model causes infertility via iron-mediated oxidative stress in mice. Redox Biol. 2020;37:101726. doi: 10.1016/j.redox.2020.101726. PubMed PMID: 32961443; PubMed Central PMCID: PMCPMC7509075.
71 Naqvi H, Sakr S, Presti T, Krikun G, Komm B, Taylor HS. Treatment with bazedoxifene and conjugated estrogens results in regression of endometriosis in a murine model. Biol Reprod. 2014;90:121. doi: 10.1095/biolreprod.113.114165. PubMed PMID: 24740602; PubMed Central PMCID: PMCPMC4093999.
72 Nakamura S, Ochiai K, Ochi A, Ito M, Kamiya T, Yamamoto H. Spontaneous endometriosis in a mandrill (Mandrillus sphinx). J Comp Pathol. 2012;147:386-90. doi: 10.1016/j.jcpa.2012.01.004. PubMed PMID: 22520805.
73 Assaf BT, Miller AD. Pleural endometriosis in an aged rhesus macaque (Macaca mulatta): a histopathologic and immunohistochemical study. Vet Pathol. 2012;49:636-41. doi: 10.1177/0300985811406890. PubMed PMID: 21521902; PubMed Central PMCID: PMCPMC3597994.
74 Nair HB, Baker R, Owston MA, Escalona R, Dick EJ, VandeBerg JL, et al. An efficient model of human endometriosis by induced unopposed estrogenicity in baboons. Oncotarget. 2016;7:10857-69. doi: 10.18632/oncotarget.7516. PubMed PMID: 26908459; PubMed Central PMCID: PMCPMC4905444.
75 D'Hooghe TM, Kyama CM, Chai D, Fassbender A, Vodolazkaia A, Bokor A, et al. Nonhuman primate models for translational research in endometriosis. Reprod Sci. 2009;16:152-61. doi: 10.1177/1933719108322430. PubMed PMID: 19208783.
76 Ferreira GS, Veening-Griffioen DH, Boon WPC, Moors EHM, van Meer PJK. Levelling the Translational Gap for Animal to Human Efficacy Data. Animals (Basel). 2020;10. doi: 10.3390/ani10071199. PubMed PMID: 32679706; PubMed Central PMCID: PMCPMC7401509.
77 Denayer T, Stöhr T, Van Roy M. Animal models in translational medicine: Validation and prediction. New Horizons in Translational Medicine. 2014;2:5-11. doi: 10.1016/j.nhtm.2014.08.001.
78 Sams-Dodd F. Strategies to optimize the validity of disease models in the drug discovery process. Drug Discov Today. 2006;11:355-63. doi: 10.1016/j.drudis.2006.02.005. PubMed PMID: 16580978.
79 Vargas E, Aghajanova L, Gemzell-Danielsson K, Altmae S, Esteban FJ. Cross-disorder analysis of endometriosis and its comorbid diseases reveals shared genes and molecular pathways and proposes putative biomarkers of endometriosis. Reprod Biomed Online. 2020;40:305-18. doi: 10.1016/j.rbmo.2019.11.003. PubMed PMID: 31926826.
80 Jones RC. The effect of a luteinizing hormone-releasing hormone antagonist on experimental endometriosis in the rat. Acta Endocrinol (Copenh). 1987;114:379-82. doi: 10.1530/acta.0.1140379. PubMed PMID: 3551430.
81 Mishra A, Galvankar M, Vaidya S, Chaudhari U, Modi D. Mouse model for endometriosis is characterized by proliferation and inflammation but not epithelial-to-mesenchymal transition and fibrosis. J Biosci. 2020;45. PubMed PMID: 32975232.
82 Nishimoto-Kakiuchi A, Netsu S, Okabayashi S, Taniguchi K, Tanimura H, Kato A, et al. Spontaneous endometriosis in cynomolgus monkeys as a clinically relevant experimental model. Hum Reprod. 2018;33:1228-36. doi: 10.1093/humrep/dey095. PubMed PMID: 29684118; PubMed Central PMCID:

PMCPMC6012197.
83 Persoons E, De Clercq K, Van den Eynde C, Pinto S, Luyten K, Van Bree R, et al. Mimicking Sampson's Retrograde Menstrual Theory in Rats: A New Rat Model for Ongoing Endometriosis-Associated Pain. Int J Mol Sci. 2020;21. doi: 10.3390/ijms21072326. PubMed PMID: 32230898; PubMed Central PMCID: PMCPMC7177935.
84 Konno R, Fujiwara H, Netsu S, Odagiri K, Shimane M, Nomura H, et al. Gene expression profiling of the rat endometriosis model. Am J Reprod Immunol. 2007;58:330-43. doi: 10.1111/j.1600-0897.2007.00507.x. PubMed PMID: 17845203.
85 Cosar E, Mamillapalli R, Moridi I, Duleba A, Taylor HS. Serum MicroRNA Biomarkers Regulated by Simvastatin in a Primate Model of Endometriosis. Reprod Sci. 2019;26:1343-50. doi: 10.1177/1933719118765971. PubMed PMID: 29587611; PubMed Central PMCID: PMCPMC6949973.
86 Kim YS, Kim YJ, Kim MJ, Lee SJ, Kwon H, Lee JH. Novel Medicine for Endometriosis and Its Therapeutic Effect in a Mouse Model. Biomedicines. 2020;8. doi: 10.3390/biomedicines8120619. PubMed PMID: 33339236; PubMed Central PMCID: PMCPMC7766695.
87 Ma Y, He YL. Study of an antiangiogenesis gene therapy with endostatin on endometriosis in the nude mouse model. Clin Exp Obstet Gynecol. 2014;41:328-34. PubMed PMID: 24992787.
88 Gupta D, Hull ML, Fraser I, Miller L, Bossuyt PM, Johnson N, et al. Endometrial biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;4:CD012165. doi: 10.1002/14651858.CD012165. PubMed PMID: 27094925; PubMed Central PMCID: PMCPMC6953323
89 Nisenblat V, Bossuyt PM, Shaikh R, Farquhar C, Jordan V, Scheffers CS, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;2016:CD012179. doi: 10.1002/14651858.CD012179. PubMed PMID: 27132058; PubMed Central PMCID: PMCPMC7076288.