

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

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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.

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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 pathophysiological 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 treatment¹⁵ 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.

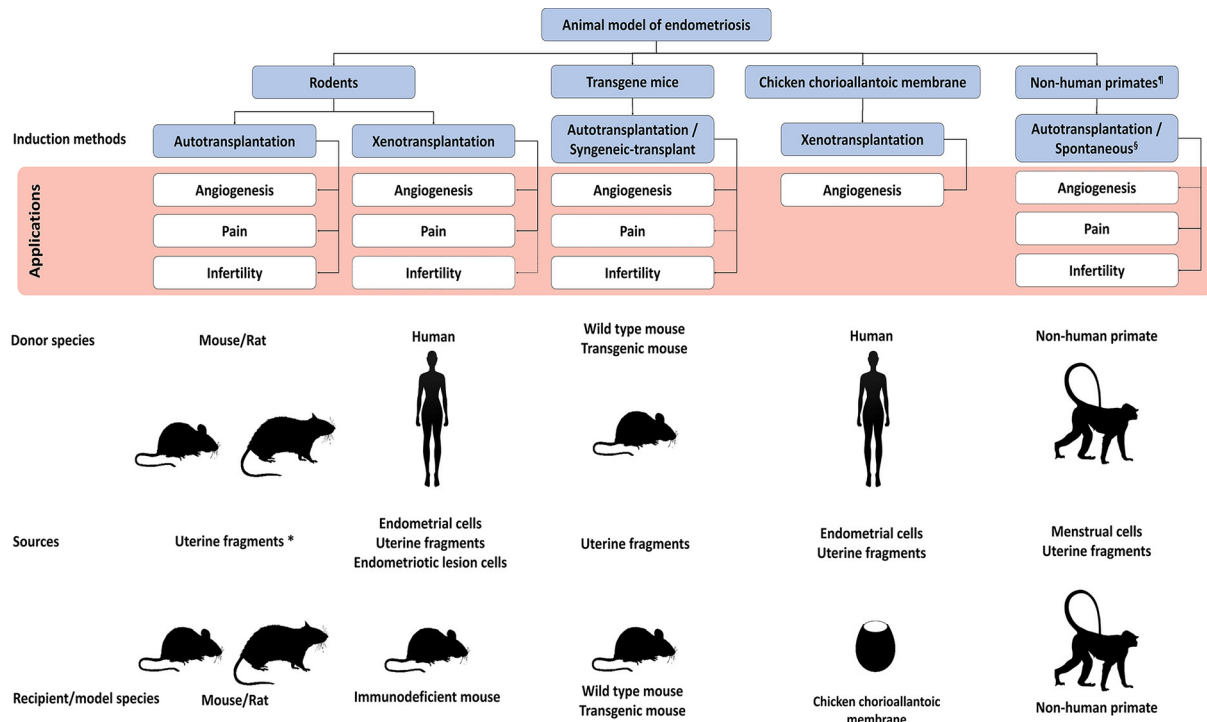


Figure 1: This figure illustrates the applications of different types of animal models in endometriosis research. [‡]Non-human primate model of endometriosis is performed in species including baboons, rhesus monkeys, marmoset monkeys, and cynomolgus monkeys. [§]Spontaneous endometriosis is reported in 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 <i>Rhesus Macaque</i>	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,

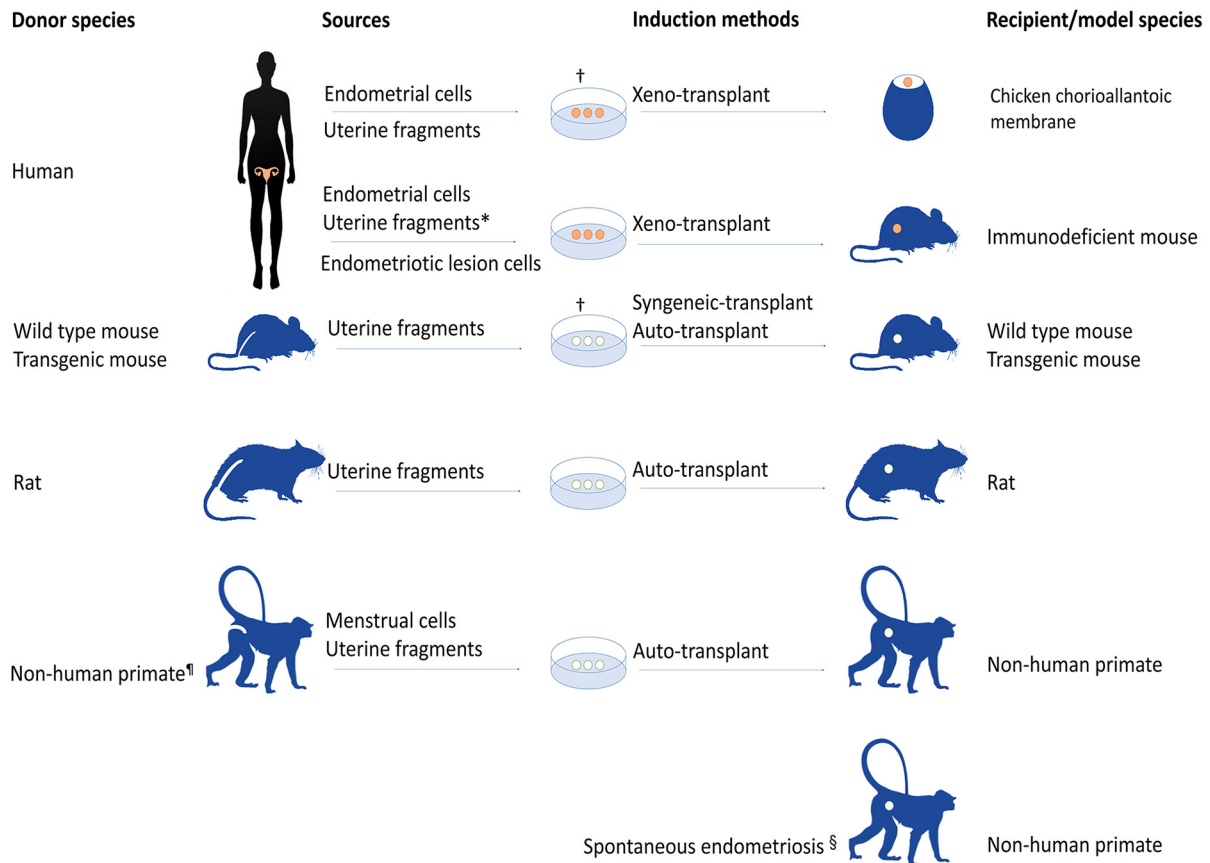


Figure 2: This figure presents different types of animal models used in endometriosis research. *Uterine tissue fragments or biopsies are used without enzymatic cell isolation. †Orange circles represent different species as the source of tissue, while white circles indicate the same species as the source 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 others²⁹ gained the highest score by providing key elements and resemblance to human endometriosis.²⁹ Greaves et al. 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 others³⁵ and Naqvi and colleagues⁷¹ 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 therapeutics⁸⁶ 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.

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