



Murine Models of Endometriosis: A Systematic Review

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Abstract

Objectives: This review inspects the usage of animal models and the practical solutions of this method for different challenges of endometriosis. The objectives of the study are to determine and compare the histopathology, biomarkers, and development of endometrial lesions in murine homologous and heterologous endometriosis models.

Methods: The literature search was performed on PubMed, Scopus, Web Cochrane, and EMBASE from January 1990 to January 2019. Experimental articles in which the establishment of the endometriosis model had been proven through the examination of size, weight, number of implants, adhesion, histologic score, and altered biomarker were eligible for inclusion.

Results: Based on type of induction, articles were categorized into two groups: heterologous-induced method (n=5) and autologous-induced method (n=13). In general, in case of establishing the heterologous induction method is less reliable than the autologous induction method.

Conclusions: Using human endometrial tissues for endometrial inductions is possible in heterologous models under immunosuppression, which is more suitable for therapeutic studies, but time limitation considerations are mandatory for this type of model. Homologous endometriosis inductions cause larger endometrial lesions, biomarkers, and reproduction rate changes similar to those occurring in humans. Similarities make this method more appropriate for pathogenesis and genetic studies and also observe the impact of endometriosis on the next generation. Choosing an appropriate model for the induction of endometriosis is dependent on the purpose of each study.

Keywords: Endometriosis, Animal models, Homologous transplantation, Heterologous transplantation

Introduction

Endometriosis is a common benign disease characterized by an ectopic presence of endometrium-like tissue in extra uterine locations in women of reproductive age. It is a chronic estrogen-dependent inflammatory condition that causes pelvic pain and subfertility and impacts many aspects of women's lives (1). The most common site for endometriosis is the ovary and peritoneum (2). Endometriosis' prevalence rate seems to be 10%, with a peak in those between 25-35 years. A high incidence of endometriosis has been reported in women with pelvic pain and infertility (20%-90%) (1-5). It is a public health problem with adverse effects on women's quality of life and an economic burden (6). The exact mechanisms in the pathogenesis of endometriosis yet remain obscure (7). Three theories have been proposed to explain the pathogenesis of endometriosis: (a) Ectopic transplantation of endometrial tissue, (b) coelomic metaplasia and (c) the induction theory (peritoneal activation of embryonic cell rests) (5,8). The recent theory explains the possibility of

rare and unusual endometriosis in men (8).

Several theories have existed about the etiology of endometriosis. However, the most robust evidenced pathogenic hypothesis is based on the retrograde menstruation phenomenon, which is not enough to develop endometriosis solely. Other factors as well must be involved to cause the disease. Biochemical and molecular disorders of eutopic endometrium, abnormal responses to sex steroids, inadequate immune responses, uterine malformations, proinflammatory peritoneal fluids, and genetic susceptibilities are counted as factors that may ultimately contribute to symptomatic endometriosis (3,5,9,10).

The shortage in our knowledge about the exact causes of endometriosis makes the treatment options restricted and more focused on the patient's symptoms of this disease. The treatments are generally based on combinations of hormonal (suppression of ovarian function) and surgical procedures. Side effects of hormone therapy usually cause one to stop taking the medication and eventually

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Key Messages

- ▶ Choosing an appropriate model for the induction of endometriosis is dependent on the purpose of each study.

relapse. Surgical procedures also could not solely cause recovery, and after more surgeries, many patients suffered recurrence (up to 70% of cases) (8,11,12). Finally, it can be stated that alteration in inflammatory status, immune responses, angiogenesis, apoptosis, and hormonal responses may occur in ways that generate the ectopic endometrial tissue.

Despite the recognition of endometriosis for centuries, the prevalence rate, its causes, and the pathogenic process are not entirely clear. Monitoring the stages of the disease is impossible without repeated invasive procedures. Due to the apparent limitations and ethical considerations in human trials, endometriosis field researchers use animal models to investigate the pathophysiology, treatment, and prevention of disease (8). One of the benefits of using animal experiments is controlling the effects of confounders such as age, menstrual cycle stages, use of medications, diets, and environmental influences.

This review studies of common animal models and their practicality in many different challenges. Prevalent studies on endometriosis induction models have been mostly descriptive reviews. Still, the objectives of the present study are to determine and compare the histopathology, biomarkers, and development of endometrial lesions in murine homologous and heterologous endometriosis models. In this systematic review, the benefits and limitations of each model have also been concluded.

Methods

This study was prepared and completed according to PRISMA guidelines (13). The systematic review has not been registered with PROSPERO because this study is limited to publication.

A search was conducted to find the most relevant studies in the English language. Reported by our two authors independently (NM, HR) the literature search was performed on Scopus, PubMed, Cochrane, and EMBASE, from January 1990 to January 2019. The terms used for the search were as follows: (“endometriosis” OR “ENDO” OR “endometriotic lesion” OR “endometriotic implant: OR “endometriotic transplant” OR “endometriotic explant”) AND (“animal” OR “animals”) AND (“model” OR “models”). Experimental articles in which the establishment of the endometriosis model had been proven through the examination of size, weight, number of implants, adhesion; histologic score, and biomarker changes were eligible for inclusion. We searched through the included studies’ reference lists and reviews for additional studies.

Experimental studies (in English language) on mice or rat model of endometriosis with one of the establishing

criteria for endometriosis model (size, weight, and the number of implants; adhesion score, Histologic score, and biomarker indices) were included in this study. Articles which were not entirely related to the main objective, review articles, and case reports were excluded.

After the primary search, two reviewers (H.H. & O.B.) screened the heading and abstract of all articles individually. Lack of consistency between the reviewers was resolved by discussion in close consultation with the senior reviewer (F.R.T.)

We extracted the data from the number One (full) reviewer (H.H.) and summarized it into a table. The other reviewer (M.S.) reviewed the extracted data, including the prime author and publication year, mice ethnicity and sample size, Induction model, Time of assessment, The purpose of the endometriosis model induction in the study.

Quality Assessment

Quality assessment and risk of bias for quantitative studies were estimated by the Quality Assessment Tool (Cochrane Public Health). The Cochrane risk-of-bias tool was used to adjudicate (high, low, or unclear) individual elements of five fields of selection, performance, attrition, reporting, and others. Each study was declared “strong” if it had met seven or more criteria, “moderate” if five or six criteria were met, or “weak” in case of four or fewer criteria being met. The quality of all relevant studies selected for this review was systematically evaluated using this checklist, independently by our two reviewers (F.R.T. & M.S.) (Table 1).

Results

The initial search yielded 748 articles. After excluding the duplicate articles, 477 articles remained for screening the title and abstract, yet not all of them met the goals of this review study, so excluded. Of the remaining 179 full-text articles, 161 were excluded due to inconsistency of their study design to inclusion criteria. Figure 1 shows the summarized PRISMA-P flow diagram of the definitive search results. We classified the 18 selected articles into two groups based on types of induction origins: heterologous-induced animal models (xenograft) for endometriosis (n=5) and autologous-induced animal models (mouse or rat graft) for endometriosis (n=13). An overview of the selected studies’ characteristics and discoveries are summarized in Tables 2 and 3.

Murine Model

In contrast with humans and other inhuman primates, endometrial tissues in rodents do not shed; thus, endometriosis does not occur naturally in them. Endometriosis must be developed through endometrial tissue transplantation in mice or rats peritoneal or subcutaneous tissues. Quantity, location, and size of lesions, as well as the histological and molecular changes,

Table 1. Risk of Bias in Individual Studies

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Total risk of bias
Awwad, 1999	●	●	●	●	●	●	●	Weak
Lu, 2006	●	●	●	●	●	●	●	Weak
Güney, 2008	●	●	●	●	●	●	●	Strong
Stilley, 2009	●	●	●	●	●	●	●	Strong
Banu, 2009	●	●	●	●	●	●	●	Moderate
Do Amaral, 2009	●	●	●	●	●	●	●	Moderate
Bruner-Tran, 2010	●	●	●	●	●	●	●	Weak
Yildirim, 2010	●	●	●	●	●	●	●	Moderate
Pelch, 2012	●	●	●	●	●	●	●	Weak
Yavuz, 2014	●	●	●	●	●	●	●	Strong
Azimirad, 2014	●	●	●	●	●	●	●	Moderate
Uzunlar, 2014	●	●	●	●	●	●	●	Moderate
Bakacak, 2015	●	●	●	●	●	●	●	Moderate
Erten, 2016	●	●	●	●	●	●	●	Weak
Ilhan, 2016	●	●	●	●	●	●	●	Moderate
Soylu Karapinar, 2017	●	●	●	●	●	●	●	Moderate
Dodds, 2017	●	●	●	●	●	●	●	Moderate
Jafarabadi, 2017	●	●	●	●	●	●	●	Weak

● High Risk of Bias; ● Low Risk of Bias; ● Unclear Risk of Bias.

are measurable after the induction of endometrial implants. Efficacious settlement of endometriosis is a multi-step process and is related to swift peritoneal attachment occurrence, extracellular matrix reduction, and neovascularization. The murine models are divided into two categories: homologous and heterologous (10).

(A) Homologous Model

In this model, the endometrium is isolated from surgically removed female murine's uterine horns (C57 black 6 (C57BL/6) or Bagg Albino Mouse (BALB/c) or Sprague Dawley rats or Wistar rats) by either cutaneous biopsy punch or physical separating. Then endometriosis induction is either executed by surgical sutures of the

endometrium to the peritoneal membrane or the injection of endometrial segments suspension into the abdominal cavity (21,31-34).

There is a variety of endometrium segments used for the induction of endometriosis in different studies. Usually, it ranges between 2 mm² and 4 mm² for mice, while 5 mm² is more appropriate for rat models. There is an inconsistency in judgments about low deviations control (2 mm² -3 mm²). The size of the endometriotic lesion affects the development of the lesion and the density of microvessels (15, 17).

To improve endometriosis modeling, a homologous model creating method has been developed by giving supplements of estradiol to ovariectomized mice, which

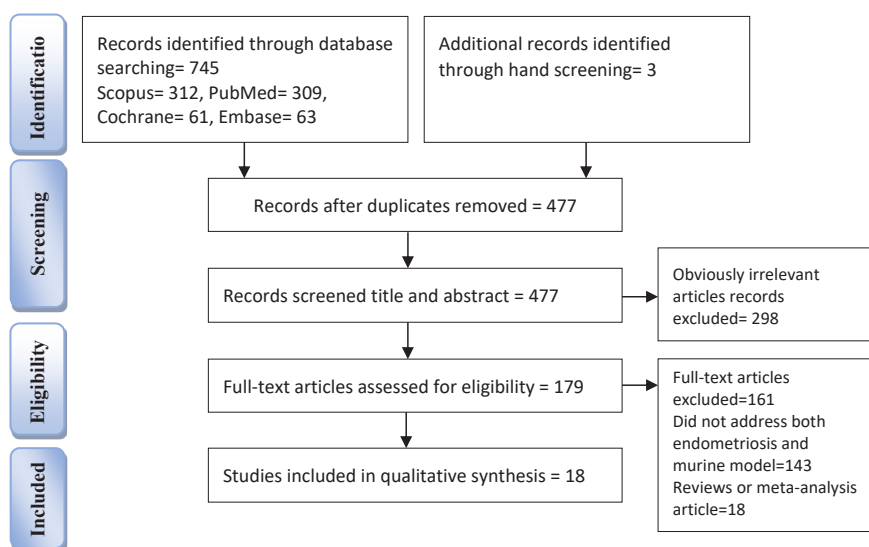
**Figure 1.** Flow Chart for Study Inclusion and Exclusion Process.

Table 2. Heterologous-Induced Animal Models for Endometriosis

Author, Year (Ref)	Mice Ethnicity & Sample Size	Induction Model	Time of Assessment	The Purpose of the Endometriosis Model Induction	Findings		Limitation	Benefits
					Growth and Number of Lesions	Marker		
Awwad, 1999 (14)	CB17 SCID mature female mice (n=55), endometrial tissue of fresh human late secretory	0.6 ml (0.8 g of wet tissue) of women's secretory endometrium injected into the peritoneal cavity on the ventral midline of SCID mice. Hormone therapy was performed at the time of injection and 5 days later in two groups: a) 17- β -estradiol-3-benzoate 30 μ g/kg IM, (b) a combination of oestradiol/progesterone (10 mg/kg)	14 days after injection	Validate the SCID mouse as an experimental model of endometriosis	The mean size of implants, mean number of implants per animal, and the displayed multiple implants in the estradiol/progesterone-treated group were significantly higher than the estradiol-treated group and were statistically significant.	N/R	It's the inability to duplicate the immune changes occurring at the implantation size in humans	It provides the opportunity to study transformational and adaptational changes occurring in the human endometrium when implanted onto ectopic host size
Lu, 2006 (15)	10 women with endometriosis and 10 control and 60 Female ICR mice	One Xenotransplantation of human endometrium into the peritoneal cavity of the immunodeficient mice model without any suture	One xenotransplantation of human endometrium into the peritoneal cavity of the immunodeficient mice model without any suture	Comparison of two models: Transplantation of women with endometriosis versus without endometriosis	N/R	The scores of VEGF and MMP-2 of viable glandular cells of transplants were increased compared with the ones before transplantation. The scores of VEGF and MMP-2 of transplants from women with endometriosis was higher than those of control women	Availability of human tissue, and by the restricted duration of culture due to the residual immunological response of the host	Understanding of the causal relationship between immune abnormalities of peritoneal cavity and endometriosis
Banu, 2009 (16)	ovariectomized nude mice, 7 mice	Four 5mm fragments were implanted with a suture in the cranial and caudal parts of the peritoneal wall to the right and left of the incision	28-35 days after induction procedure	A potential experimental a tool to study the molecular pathogenesis of endometriosis in humans	A mean number of 6.43-0.30 per mouse were identified. The mean number of single and multiple endometriosis-like lesions were 4.23-0.56 and 2.00-0.31, Respectively. The mean size of endometriosis like-lesions was 0.49-0.02 cm	COX-2, PGE2, PGE4, and ER α protein was expressed abundantly in both glandular epithelial and stromal cells	Age-related compensatory immunity	Use of these human endometriosis cells in xenograft models provides an excellent opportunity to study functional genomics, experimental therapeutics, cellular trafficking, and organization of endometriosis glands.

Table 2. Continued

Author, Year (Ref)	Mice Ethnicity & Sample Size	Induction Model	Time of Assessment	The Purpose of the Endometriosis Model Induction	Findings		Limitation	Benefits
					Growth and Number of Lesions	Marker		
Bruner-Tran (17), 2010	Biopsy of endometrial tissues (n=8), Rag2 γ (c) mice (n=27)	Human tissues during the proliferative phase were injected into castrated mice intraperitoneally below the umbilicus. Some mice additionally received human leukocytes (2.5*10 ⁶ cells/100 mL of PBS each) 24 h before the human tissue injection	10 to 12 days after the injection of human tissue	Endometriosis immunocompromised mice model and after the transfer of human leukocytes	Statistically significant reduction in the severity of peritoneal disease (Proportion of mice with lesions, Number of lesions per mouse, Total volume of all lesions per animal (mm ³), and Average volume of individual lesions (mm ³)) in rag2g (c) mice, which also received adoptive transfer of human immune cells compared with mice that did not receive immune cells.	N/R	The immunocompromised status of the host animal, Animals with more aggressive behavior	This model will allow the examination of the impact of specific populations of immune cells on the development of experimental disease
Jafarabadi (18), 2017	The human endometrial samples (n=6); 16 female NMRI mice with γ -irradiated	In model A (human endometrial tissue fragments): 3 pieces of endometrial tissue fragments (1-2 mm ³) subcutaneously on one side of the gluteal region In model B (human endometrial mesenchymal cells); 20 μ L of endometrial cell suspension containing 2*10 ⁶ cells was injected subcutaneously on one side of the gluteal region. The mice were treated with a single dose of 7.5 Gy γ -irradiation for 6 min 72 h later, the tissue and cells	20 days after transplantation	Evaluation of two endometriosis models by transplantation of human endometrial tissue fragments and human endometrial mesenchymal cells	N/R	The gland sections per cubic millimeter, the expression of OPN and MMP2 genes, and the level of 17- β estradiol were higher in model B than model A (P=0.03)	Animals with more aggressive behavior	It also provides a promising tool not only for experimental approaches evaluating the etiology of endometriosis regarding the type of responsible stem cells but also for therapeutic testing of pharmacological and hormonal modulations

SCID: Severe combined immunodeficiency; ICR mice: Institute of Cancer Research mice; Rag2 γ : Recombinant activating gene 2/common cytokine receptor γ chain; VEGF: vascular endothelial growth factor; MMP-2: matrix metalloproteinases-2; COX-2: Cyclooxygenase-2; EP2:PGEP2 Prostaglandin; PGEP4: Prostaglandin EP4; Era: Estrogen Receptor α ; OPN: Osteopontin; N/R: Not reported

Table 3. Homologous-Induced Animal Models for Endometriosis

Author (Ref)	Mice Ethnicity & Sample Size	Induction Model	Assessment Time	The Purpose of the Endometriosis Model Induction	Findings		Adhesion & Histologic Score ^a	Fecundity Result	Limitation	Benefits
					Growth and Number of Lesions	Marker				
Güney (19)	Female Wistar albino rats, 25 rats	Endometriosis was surgically induced by a 5*5 mm fragment of uterine tissue onto the inner surface of the abdominal wall	4 and 8 wk after transplantation	Treated with melatonin	Implant growth rate (volume and weight) at 4 and 8 wk after induction surgery confirms endometriosis model	COX-2 positivity, the endometrial explant levels of MDA, activities of SOD and CAT at 8 wk after induction surgery confirms endometriosis model	Preservation of epithelia at 8 wk after induction surgery confirms endometriosis model	-	Generalization of results from autologous animal studies to women with endometriosis	Use of the histologic, immunohistochemical, and biochemical findings showing morphologic degeneration changes
Stilley (20)	Mature female Sprague-Dawley rats, 54 ENDO, and 40 Sham rats	Four 2 mm ² implants were auto transplanted to the arterial cascades of the small intestine, begins at the cecum	4 wk after surgery and (Day 1) to collect zygotes, on Day 5 to collect preimplantation embryos/ blastocysts, or on day 15 of gestation to evaluate pregnancy loss	Effects of endometriosis on fecundity		Significantly more TIMP1 was measured in the peritoneal fluid of Endo rats compared with Sham rats		See footnote ^a	It is not useful for examining early events of endometriosis development	This model of endometriosis induction is useful for long-term studies, including evaluating fecundity status
Do Amaral (21)	Female, adult and virgin Wistar rats, 30 rats	A 5 × 5 mm section was sutured to the abdominal wall on the right flank next to a blood vessel	1 and 2 months after the transplantation	Development of an experimental model	No statistically significant difference was found in the surface area of the induced lesions in two groups (group 1 was reoperated in 30 days, and group 2 in 60 days)				The actual correlation of experimental foci of endometrial tissue with human endometriosis is unknown	In this model, evaluation of the implants is feasible
Yildirim (22)	Female, nonpregnant, nulligravid Wistar-Hannover albino rats, 30 rats	Four 6*3 mm pieces were implanted into the peritoneal the surface of the right and left abdominal walls	2 wk after induction	The effects of letrozole and melatonin	After 2, 4, and 6 wk, the mean volume of implants showed a successful endometriosis induction model.		The mean histopathological score of implants after 2, 4, and 6 wk showed a successful endometriosis induction model.			
Pelch (23)	Mice, 20	Three 2 mm ² biopsies are sutured to an artery in the arterial cascade of the intestinal mesentery	4 and 8 wk after induction	Mouse Model of Surgically-induced Endometriosis	At one-month post-induction fluid-filled and lanced endometriotic lesion weight were significantly correlated				Limitations associated with the surgical induction of endometriosis	The model used to study the etiology, pathology, and risk factors of endometriosis

Table 3. Continued

Author (Ref)	Mice Ethnicity & Sample Size	Induction Model	Assessment Time	The Purpose of the Endometriosis Model Induction	Findings		Adhesion & Histologic Score ^a	Fecundity Result	Limitation	Benefits
					Growth and Number of Lesions	Marker				
Yavuz (24)	Adult female Wistar rats, 35 rats	A 0.5 × 0.5 × 0.1-cm piece from the right uterine horn was attached to the peritoneum only on the right side of the ventral abdominal wall close to an artery	3 and 4 wk after induction	Effect of resveratrol	The mean volume of implants after 3 and 4 wk showed a successful endometriosis induction model.	Explant levels and serum level of SOD, MDA, and GPx at 4 wk after induction surgery confirms endometriosis model			To develop a model of endometriosis, mice must undergo surgery, a small number of rats per group	The model used to pharmacological treatment of endometriosis
Uzunlar (25)	Female, non-pregnant Wistar albino rats, 24 rats	A 5*5-mm fragment was implanted onto the inner surface of the right side of the abdominal wall close to an artery	4 and 7 wk after the induction procedure	Effects of repeated propranolol administration	The mean volume of implants after 4, and 7 wk to examine the endometrial implants for size and viability	Explant H score of VEGF, MMP2 epithelium and stroma, MMP9 epithelium, and stroma at 7 wk after induction surgery confirm endometriosis model	The mean histopathological score of implants after 7 wk showed a successful endometriosis induction model.		Have not used intra-vital imaging methods to measure blood flow of endometrial tissue	This model is a suitable study on the effectiveness of therapeutical drugs and chemicals. It also provides the opportunity to monitor the development of ectopic lesions at different time intervals
Azimirad (12)	Mature, nulligravid, female Sprague–Dawley rats, 23 rats	4 pieces of endometrial tissue were fixed on the most vascularized areas of the peritoneum	6 wk after transplantation	Effect of thalidomide		Counts of leukocytes, lymphocytes, VEGF-A, and IL-6 at 4 wk after induction surgery confirms endometriosis model	The mean histopathological score of implants after 6 wk showed a successful endometriosis induction model.		The small number of the participating subjects	The model used to endometriosis therapeutic
Bakacak (26)	Wistar-Hannover albino nulligravida female rats, 16 rats	Four 2 mm ² of the endometrial surface were sutured to regions of intense vascularization on the intraperitoneal surface, 50 µg/kg Estradiol Depot was administered to all rats	2 and 4 wk after induction	The effects of thalidomide	The mean weight volume of implants after 4 wk showed a successful endometriosis induction model.	Examination of pre- and post-treatment values of oxidative marker (MPO, GPx, CAT, MDA, SOD, NO) and VEGF-A levels received from the peritoneal washing materials of the rats at 2 and 4 wk after induction surgery confirm endometriosis model	The mean histopathological score of implants after 4 wk showed a successful endometriosis induction model.		immunohistochemical evaluation was not performed	The model used to endometriosis therapeutic
Erten (27)	Sexually mature, cycling, female Wistar albino rats, 33 rats	A 0.5*0.3 cm tissue fraction was sutured to the inner surface of the peritoneum on the right side of the abdomen	3 and 6 wk after the transplantation	Effects of vitamin C	The mean weight volume of implants after 3 and 6 wk showed a successful endometriosis induction model.		The mean histopathological score and Masson's trichrome score of implants after 6 wk showed a successful endometriosis induction model.		Rats are different from women regarding reproductive biology and anatomy	Autotransplantation of uterine tissues directly to the peritoneal wall was the only a technique that achieved developing endometriotic implants made up of both glands and endometrial stroma

Table 3. Continued

Author (Ref)	Mice Ethnicity & Sample Size	Induction Model	Assessment Time	The Purpose of the Endometriosis Model Induction	Findings		Adhesion & Histologic Score ^a	Fecundity Result	Limitation	Benefits
					Growth and Number of Lesions	Marker				
Ilhan (28), 2016	Female, nonpregnant, Sprague-Dawley rats, 18 rats	A fragment of endometrial tissue separated from the myometrium was sewn around the blood vessel into the abdominal wall	Four and eight wk after the transplantation	Effects of A mixture of St. John's wort and sea buckthorn oils	The mean volume of implants after 4, and 8 wk showed a successful endometriosis induction model.	level of TNF- α , VEGF and IL-6 at 4 and 8 wk after induction surgery confirms endometriosis model	The mean adhesion score of implants after 4, and 8 wk showed a successful endometriosis induction model		To develop a model of endometriosis, mice must undergo surgery	The model used to endometriosis therapeutic
Karapinar (29), 2017	Female adult Wistar albino rats, 20 rats	A 5*5-mm fragment was implanted onto the right side of the ventral abdominal wall close to an artery	four and six wk after the transplantation	Effect of Dexpanthenol	The mean volume of implants after 4, and 6 wk showed a successful endometriosis induction model.	explant levels and serum level of TAS, TOS, and OSI and TNF- α at 4 and 6 wk after induction surgery confirms endometriosis model	Histopathologic score (both ST and GT scores): After 6 wk; it showed a successful endometriosis induction model		To develop a model of endometriosis, mice must undergo surgery	The model used to endometriosis therapeutic
Dodds (30), 2017	(C57BL/6; n = 43 donors and 43 recipients) and BALB/c (n = 38 donors and 43 recipients)	Donor mice uterus were removed, and the endometrium was dissected. The amount of endometrium was collected (7.5, 15, 25, or 40 mg) Recipient mice of syngeneic strain and identical estrous stage were intraperitoneally injected with the donor	21 days after transplantation	Effect of the natural estrous cycle, mouse strain, and varying amounts of donor endometrial tissue	C57BL/6 mice were more likely to develop dense-type lesions, whereas BALB/c mice developed a greater proportion of cystic type				Immune responses of the wild-type mice used in this study may not have been inappropriate. Their different genetic regulation may result in the activation of distinct inflammatory cells, signaling cascades, and mediators that ultimately determines the endometrial debris fate.	Examples of potential applications include maternal or early life influences of lesion development, the impact of surgical removal of lesions, contributions to and consequences of pain and central sensitization, and the effect of lesions on fertility. With such possibilities, this model may be useful for studying new molecular targets and therapeutics ultimately providing better treatment outcomes for women often long-suffering with endometriosis.

^a Significantly fewer antral follicles and fewer corpus luteum were present in Endo rat ovaries than in Sham rat ovaries. Luteinized unruptured follicles were observed in 50% of the ovaries from Endo rats, whereas 0% of the Sham had LUFS
 COX-2: cyclooxygenase-2; VEGF: Vascular endothelial growth factor; MDA: Malondialdehyde; SOD: Superoxide dismutase.; CAT: catalase; ENDO: Endometriosis; TIMP1: Tissue inhibitor of metalloproteinase-1; LUFS: Luteinized unruptured follicle syndrome; GPx: Glutathione peroxidase; VEGF: vascular endothelial growth factor; MMP: matrix metalloproteinases.; IL-6: interleukin-6; MPO: myeloperoxidase; NO: nitric oxide; TNF- α : Tumor necrosis factor- α ; TAS: Total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index; ST: stromal tissue; GT: glandular tissue; C57BL/6: C57 black 6; BALB/c: Bagg Albino Mouse

creates green fluorescent protein expressions on the group and makes it easier to identify sites and sizes of endometrial lesions for harvesting surgeries. Then a suspension containing minced tissue of the green endometrium will be injected into an ovariectomized mice group (18).

1. Limitation

Since rodents do not spontaneously develop endometriosis and do not menstruate, the conditions of human patients differ from rodent models, which makes the autologous model of rodents an unreliable reflection of the situation in humans (10). In most experiments, the separation between myometrium and endometrium wasn't performed. Therefore, both sections were planted. It caused the measurements of size and weight of the lesions to be considerably influenced by the presence of the myometrium, which made those studies dissimilar in conditions compared to the humans. Rarely in the studies performed on mice and rats, the endometrium has been obtained in isolation from the myometrium and solely implanted, which may affect the lesions' developments (34).

2-Benefits

Due to the critical role of the immune system in the progression of endometriosis, autologous models of rodents with intact immune systems create an opportunity to better understand the pathophysiology of endometriosis. This makes it possible to observe and analyze the cross talk of peritoneal endometriotic cells and the immune system, which is proven to play a significant role in humans (31, 33).

The expenses for creating rodent models are significantly low. It provides opportunities for performing experiments in vast groups of animals with genetic similarities. No rejection probability of ectopically auto transplanted tissues makes it easier to perform long-term studies on the matter. This type of model is accurately useful to examine the involvement of mechanisms in the peritoneal attachment of endometrium and also to study therapeutic drugs and chemicals effectiveness. It is also suitable for monitoring the progression of the ectopic lesion at different intervals of time. Furthermore, as the homologous model has the advantage of a well-characterized immune system, it is suited to investigate the effects of anti-inflammatory agents and immunomodulating drugs on endometriosis. More importantly, to investigate single roles of genes, transgenic models of mice are usable as endometriosis models, which creates new insights into endometriosis' etiology (10, 34).

Our search strategy finally selected 13 studies that had used autologous or syngeneic (genetically identical, or sufficiently similar and immunologically compatible with transplantations) rodent groups to induce endometriosis. In terms of endometriotic development, adhesion, Histologic score, Fecundity, and biomarker change, results

are summarized in Table 2.

3-Endometriotic Lesions Development

Most of the studies reported growth rate changes of endometrial-like tissues have been reported in. In any development case in endometriotic implants, the implant's dimensions were measured using a caliper. Between the second and third surgeries, the volumes of the lesions had been evaluated in the studies (2-6 weeks). Most of the studies show increases in the size of the implants between the second and third surgeries (19,21,22,25-30).

Volume decreases of the lesions have been observed in just two of the studies. One of those studies shows a tiny decrease of 4.5 mm³ in the lesion volume (19), but in the other one, the reduction is reported by the area of 12 mm² (21). Weights of the implants are measured in only two of the studies. In one of them, the weights of the implants after eight weeks of endometriosis induction are reported to be 158.7 ± 27.1 (22), but in the other one, the weight of the implant was 6.48 gr in the second surgery and 16.51 g in the third surgery (23). The type of specimen (rats vs. mice) and the size of the induced implants (2 mm vs. 5 mm) may have caused this discrepancy.

The results of another study showed that another study revealed that endometriosis-like lesions are overall more probable to develop in proestrus than estrus, and this probability gets higher with bigger masses of donor tissues. Likewise, the total number of lesions (0-3) was increased by greater masses of tissues (7.5-40 mg), which was significantly massier for proestrus C57BL/6, unlike BALB/c mice. Mice strains also altered the dominant lesion type; it was more likely for C57BL/6 to grow dense lesions, while BALB/c mice significantly developed a higher percentage of cystic lesions (30).

4. Adhesion Scores Changes

Only one of the studies evaluates the adhesion score of endometrial lesions. In this study, 4-8 weeks after endometriosis induction, the increase of adhesion scores had been concluded (28).

5. Histological Scores

The gold standard for the diagnosis of endometriosis (induction of endometriosis in mice) is the following findings:

Morphological diagnosis of endometrial glandular and stromal tissue valued as follows: 3 = well-preserved epithelial layer; 2 = moderately preserved epithelium with leukocyte infiltrate; 1 = poorly preserved epithelium (only occasional epithelial cells); and 0 = no epithelium, and fibrous tissue formation is evaluated using Masson's trichrome stain: Grade 0, no fibrosis; Grade 1, slight fibrous tissue development; Grade 2, abnormal fibrous tissue growing; and Grade 3, concentric fibrosis and hyalinization.

In 7 studies, histologic scores were evaluated to confirm

successful inductions of endometriosis. In 6 studies, the samples of the endometrial implant are scored based on preserved epithelium cells (the scores are valued between 2 and 3) (12,19,22,25-27). One of the studies has also calculated the trichrome fibrosis score and the histological score (27). At the same time, in another one, a scoring system is used to assess the glandular tissue and stromal tissue in histopathologically examined endometriotic implants at high-power field under microscopic evaluations (29).

6. Effects of Endometriotic Implants on Fecundity and Ovarian Function

Endometriosis has affected fecundity in a significant manner. Spontaneous fetal absorption/ resorption sites have been detected in 50% of the endometriosis rats, whereas none of the Shams had Spontaneous fetal Absorption/resorption sites. Compared to the shams, fewer gestational sacs and viable fetuses have been found in the Endo rats. Only one of the studies evaluates the endometriosis effects on fecundity in rats with surgically-induced endometriosis at gestational day 15 and compares it to the sham-operated controls. Less significant antral follicles and corpus luteum in the Endo group have been witnessed compared to the Sham group in this study. Luteinized unruptured follicles have been detected in 50% of the Endo rats' ovaries, whereas none of the Shams had luteinized unruptured follicle syndrome (20).

7-Biomarker Changes

Various biomolecular changes in endometriosis are engaged in the progression of lesions, counting damaged immune system responses, increased cytokines pro-inflammatory mediators, and amplified angiogenic activities (35). Therefore, investigations of biomarkers are evident in many studies to confirm the induction of endometriosis in murine models.

Endometriosis formations happen more frequently when the oxidant/antioxidant balance is disordered in favor of oxidative stress and the concentration of stress markers in peritoneal fluids increases (24).

Nine of the articles that are included in this review study contain evaluations of biomarkers to confirm endometriosis in mice or rats with the following descriptions. Some of the articles reviewed in this study indicate the suppression of peritoneal fluid and tissue antioxidants levels including catalase, superoxide dismutase, glutathione peroxidase, nitric oxide, total antioxidant status and increase oxidized lipoproteins such as malondialdehyde and myeloperoxidase and also oxidative stress index and total oxidant status in peritoneal environment and tissues of induced endometriosis in murine (19,24,26,29). However, in one of the studies, contradictory declines of malondialdehyde have been reported (26).

Some other of the articles have confirmed the elevations

of pro-inflammatory mediators and angiogenic activity such as vascular endothelial growth factor (VEGF), tumor necrosis factor- α (TNF- α), and interleukin-6 in the peritoneal environment of the rats involved with endometriosis (12,25,26,28,29). Conversely, in one of these articles, no enhancement of TNF- α has been detected in endometriotic rats, contrary to the disease's behavior (12).

Results from one study showed higher levels of tissue inhibitor of metalloproteinase-1 in their peritoneal fluid for Endo rats compared to the Shams (20). Evaluation of matrix metalloproteinases-2 (MMP2) and matrix metalloproteinases-9 levels in stroma and epithelium in one of the studies have shown an increase in endometrial implant specimens (25).

(B) Heterologous Model

Heterologous models are immunocompromised rats subcutaneously or intraperitoneally injected with human endometrial explants. The induction steps are similar to Homologous models (21,33,34,36). Immune-deficient athymic nude (lack T-lymphocytes, severe combined immunodeficiency [SCID] lack B- and T-lymphocytes, recombinant activating gene 2/common cytokine receptor γ chain double null) mice and non-obese diabetic background (NOD)-SCID mice have been used in heterologous models of endometriosis (8,31,33).

In xenotransplant models to support the development of endometrial tissue of humans in the model, supplies of exogenous human estradiol are given to immunodeficient mice. Endometriotic lesions were found in all mice of the model for athymic nude mice or SCID mice with natural killer cell suppression. Virani showed that murine implants of the endometrium were histologically comparable to endometriotic lesions in humans. The model summarized the histomorphology of the disease in humans (37).

Maintaining planted human tissue for a lengthy period is hard work, making the heterologous rodent model with a limited time frame. In the majority of the experiments, nude mice could not keep their human endometrium culture longer than 4 weeks. Lymphocyte infiltrations and dedifferentiation parameters were observable after three weeks of transplantation (34).

1-Limitations

The aspect of the immune system, which holds a significant role in the progression of endometriosis disease, is lost due to the usage of immunodeficient mice in heterologous models (33,34). A major flaw in heterologous rodent models is the limited lifespan of the transplanted human tissue, which makes the human endometrium unable to persist further than 4 weeks in nude mice (10,38).

2-Benefits

To assess the endometriosis etiology and evaluate the effectiveness of hormonal modulations and therapeutic drugs, inexpensiveness and obtainability are favorable

tools for experimental approaches. This model also makes *in vivo* drugs' efficiency inquiry in the ectopic tissue of humans possible while imitating the status of the humans' hormones during the menstrual cycle and making long-term studies unachievable in women. Besides, using fluorescence makes *in vivo* imaging possible, which enhances the ectopic lesions' number and size quantification using magnetic resonance imaging (34).

To prevent the implantation of ectopic endometrium and its growth, this model is widely used to study the effects of antiangiogenic compound. Besides, this heterologous model creates the possibility to examine the mechanisms of biological cells in reaction to drug treatment of endometrial tissue in humans. In nude mice, the suppression of matrix metalloproteinases could be restraining the ectopic lesions establishments. According to the immune system's role in the development of endometriosis, the concurrent transplantation of human endometrium alongside the injection of the non-endometriotic donor's immune cells has proved to limit the development of the disease in the intraperitoneal area of the receiver rodent (10).

We selected four of the studies that had used heterologous models to induce endometriosis. In terms of growth rate, adhesion and histologic score, Fecundity, and biomarker changes, results were summarized in Table 2. Efficacious settlement of endometriosis is a multi-step process related to swift peritoneal attachment occurrence, extracellular matrix reduction, and neovascularization (8).

3. Hormonal and Biomarker Changes

Increases in MMP-2 have been reported in an endometriosis heterologous mouse model with t-lymphocyte immunity, and two endometriosis models with transplantations of human endometrial mesenchymal cells (model B) in comparison with implanted human endometrial fragments (model A) to γ irradiated mice (15,18).

In one of those studies, in addition to MMP-2, the VEG scores of transplanted were increased compared to those before transplantations. Endometrium transplants of the endometriosis patients cause more VEGF and MMP-2 than the endometria obtained from the female control humans, suggesting that VEGF and MMP-2 may expedite the formation of endometriosis in its primary stage (15). Also, the level of 17 β -estradiol is reported significantly increased in model B compared to model A, and in both of those models considerably higher than in the control group (18).

4. Endometriotic Development

The size and number of endometriotic lesions were evaluated in three studies (14,16,17). One of them shows that 100% of the mice that received human endometrial tissues absent human immune cells exhibited induced endometriosis. Though, 56% of the mice which received

endometrial tissues alongside autologous human immune cells were reported free of induced endometriosis (or experimental disease) (17).

In another one of the studies, smaller mean sizes of the implants, less multiple, and fewer implants per SCID mouse are reported in the estrogen-treated group than the estrogen/progesterone-treated one (14). In the third study, a total of 45 endometriosis-like nodules with a mean number of 6.43 ± 0.30 per mouse were recognized in seven of the nude mice with 31 (68.89%) single lesions and 14 (31.11%) multiple lesions (16).

Discussion

Due to the apparent boundaries and ethical considerations towards human experiments, endometriosis researchers heavily rely on rodent models to investigate the pathophysiological elements of the disease. According to the lack of definitive treatments and, most importantly, limited knowledge about the disease's etiology, researchers have tried to find animal models to add fragments of evidence to help recognize the pathogenic mechanisms, and find innovative approaches for the treatment of the disease. The most crucial difference between these models and humans is that mice, rats, rabbits, and hamsters do not grow endometriosis naturally and spontaneously.

In this article, a summary of the factors affecting the success rates of rodent endometriosis inductions in two types of heterologous and homologous induction models was studied. In the reviewed studies, mice used for heterologous induction of endometriosis included athymic (nude) mice, SCID mice, and recombinant activating gene 2/common cytokine receptor γ chain double null mice. Rodents used for the homologous method in one of the studies were Recipient mice of syngeneic strain (C57BL/6 and BALB/c) with intraperitoneal injections of endometrial tissue fragments of donor mice. In 12 of the other studies which used autologous endometriosis inductions, nine studies used Wistar rats, 2 of them used Sprague-Dawley rats, and one used mice for their induction models.

In other studies, it can be seen that the mouse strains were selected based on the study objective. For instance, Dodds et al in their study, they concluded that even the prevailing lesion type differs from one mouse strain to another. C57BL/6 mice were more probable to grow dense-type lesions, while BALB/c mice developed a higher percentage of cystic type (30). Also, the cost of a heterologous study is much higher than the autologous one due to immunocompromised mice.

The results of the studies investigations show that the numbers of single and multiple lesions in heterologous endometrial induction models are higher than that of autologous models, which could be caused due to tissue induction method differences because heterologous models are more intraperitoneally injected with the endometrial fragment suspensions of women with and

without endometriosis. While in autologous methods, the endometrial tissue of one of the uterine horns of the same mouse is used for grafting, so the amount of the lesions and the grafts are equal. The growth of the lesions in autologous models is more considerable than those in heterologous models (approximately 2.2 mm³ vs. 109 mm³, respectively). Other studies use visual inspection of the pelvis during a laparotomy to identify successful endometriosis inductions (39). The endometriosis lesions are usually being counted with the help of a dissecting microscope, a caliper measure lesions. Macroscopically, endometriosis-like lesions are classified into two classes of single and multiple; single lesions consist of one visible nodule, whereas multiple lesions consist of more than one visible nodule (16).

Macroscopic aspects of the endometriosis differ based on the day of observation. The following microscopic findings confirm endometriosis: 1) several mature endometrial glands which are similar to those detected in the topical endometrium, with few endometrial stroma surrounding them, 2) exuberant granulation tissue around endometriotic foci, 3) areas of fibrosis and sporadic hemorrhagic foci, and 4) marked presence of adipose tissue (40).

Investigation about the studies included in this review article shows that the reliability of establishing a model of endometriosis induction in the heterologous induction method is much more limited than the autologous induction method. Of the five studies in this model, three studies have examined the changes in the growth of the lesions, and two of them have only examined some of the biomarkers. In contrast, most of the studies that have used autologous induction models have examined multiple methods to confirm successful endometriosis inductions (growth rate, adhesion, Histologic score, fecundity, and biomarker changes).

Recent studies reveal that the peritoneal fluids of the women infected with endometriosis contain an elevation in the number of activated macrophages that secrete local products, such as growth factors, inflammatory cytokines, and possibly free oxygen radicals (24,41). Based on the literature, raised levels of TNF- α in peritoneal fluid of patients with endometriosis stimulate the adhesion and implantation of ectopic endometrial cells to the peritoneal walls. Interleukin-6 is an essential regulator of inflammation and immune reactions. It is released locally by ectopic endometrial implants and new advanced endometrial foci and contributes to neovascularization of the implants of endometriosis. Interleukin-4 is released locally and stimulates the proliferation of endometriotic tissue, promoting the formation of adhesions in the course of endometriosis. Furthermore, it has a synergistic effect with TNF- α in the induction of the mentioned proliferation (42).

Endometriosis rats' ovaries have fewer antral follicles and corpus luteum and more luteinized unruptured follicles

than Sham rats. Consistent with these observations, the endometriosis rats develop fewer zygotes, ovulate fewer oocytes, have fewer viable fetuses at gestational day 15, and lose more pregnancies than the Sham rats. Besides, Vernon and Wilson, who developed this endometriosis model, have reported significant reductions of about 48% in the number of pups at term by the induction of endometriosis (43).

One of the limitations faced by this review was the variety of methods used in researching the articles included in this study, which made many of the findings incomparable. Another limitation was the limited number of studies that were merely performed to investigate the endometriosis induction method in mice or rats, so we included articles with the primary purpose of treatment, etiologic evaluation, or complications that confirmed endometriosis induction. Therefore, regular and systematic studies with similar conditions are suggested to compare different types of endometriosis induction models.

Conclusions

As described for humans' adverse effects of ectopic endometrial lesions can also be confirmed in animal models. Studies included in this review alongside numerous other studies with the use of murine endometriosis models highlight the essential contributions these animal models continue to make for us to understand the pathophysiology of this disease.

In this study, the number, extent, and adhesion of implants, reproductive changes, histological changes and biomarker changes associated with endometrial lesion development in murine endometriosis models were compared and evaluated. In heterologous models of endometrial induction by immunosuppression, the use of human endometrial tissue is possible, so the model developed is more similar to human endometriosis and is more suitable for therapeutic studies and evaluation of its effect, but time limitation in this model should be considered. Therefore, this model is not suitable for investigating the pathogenesis of the disease. Homologous models of endometriosis are more similar to humans in case of the disease conditions because of their larger endometrial lesions than autologous ones. Long-term studies for pathogenesis studies, genetic studies, and the impact on the next generation are also more possible because of homologous models. Choosing an appropriate model for the induction of endometriosis is dependent on the purpose of each study.

Appropriate use of each model of murine endometriosis induction will result in (a) A broader understanding of the role of tissue for genetic and epigenetic alterations to investigate the probability of disease in future generations. (b) Understanding the mechanisms that contribute to the development of the disease will open up opportunities to developing therapeutic strategies that are more effective

and with fewer side-effects, and (c) Identifying the factors that make a person susceptible to endometriosis, which can play an essential role in preventing the disease.

Authors' Contribution

MS, NM, and FRT conceived the project and provided methodological and content expertise. HH prepared and ran the search on bibliographic databases. Once the search was complete, HH and OB independently screened all titles and abstracts and full-texts and discrepancies were resolved through mutual discussion or adjudication by FRT when required. Data were extracted by HH. HH designed and ran the search strategy in conjunction with HR and FF. HH created figures and tables and wrote and revised all drafts of the manuscript, under MS's supervision. All authors reviewed the final version of the manuscript.

Conflict of Interests

The authors declare that they have no conflict interests.

Ethical Issues

Not applicable.

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