

Endometriosis related sex steroid hormones, hypothalamic pituitary gonadal axis hormones and related animal modeling: A comprehensive review of published articles and endometriosis induction methods from 2010 to 2021 with scoring based approach

Aria Salehpour (✉ ariasalehpour98@gmail.com)

Bushehr University of Medical Sciences <https://orcid.org/0000-0002-6592-5202>

Afshin Zare

Bushehr University of Medical Sciences

Arezoo Khoradmehr

Bushehr University of Medical Sciences

Mahdi Mahdipour

Tabriz University of Medical Sciences <https://orcid.org/0000-0002-2729-4593>

Amin Tamadon

Bushehr University of Medical Sciences <https://orcid.org/0000-0002-0222-3035>

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Abstract

Endometriosis is an enigmatic gynecological disease initiated by the ectopic growth of endometrial tissue and causes critical symptoms such as chronic pelvic pain, cyclic menstrual pain, subfertility or infertility. Considering extensive investigations for explaining the underlying pathophysiology of endometriosis, origin and distinctive processes which lead to endometritic state are not completely understood. In this comprehensive review, studies published from 2010 to 2021 are reviewed in order to provide a bright insight through the applications of translational animal models and endometriosis induction methods for evaluation of endometriosis pathogenesis and treatment. We provided method based inclusion criteria and reviewed all hormone-based studies with concentration on animal models. Additionally, studies with novel induction methods and approaches are categorized separately and analyzed by a novel scoring table for suitability of further investigations. Eventually, our scoring system suggested that the best-evaluated animal model for hormone related endometriosis studies is an “unopposed estrogenicity baboon model of endometriosis”.

1. Background

Endometriosis is distinguished from other diseases by benign presence of functional endometrial tissue outside the uterus. Its symptoms include chronic pelvic and cyclic menstrual pain and infertility. The prevalence in women is generally considered to be 1–5% (1). Although different mechanisms of endometriosis generation have been studied thoroughly, the processes which lead to development and maintenance of endometriotic state have not been completely understood yet. The development of new surgical methods and medications for the prevention, elimination of disease or its recurrence, necessitate defining the pathophysiological mechanism.

Since endometriosis is a multifactorial disease and these risk factors cannot exclude each other for the explanation of pathophysiology of this disease, various models and approaches were proposed (2). Widely accepted pathophysiological aspects can be classified as inflammation (3), immunological factors (4), environmental factors (5), genetics (6), pain (7), infertility (8) and hormones which is explained extensively in the following text. 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 old “retrograde menstruation” (9)!

Estrogen-dependency of endometriosis has been well documented in copious studies (10) and drugs that reduce or suppress sex steroid production in ovaries for endometriosis treatment (11) or relief of its symptoms such as pain (12) have been proposed. One of the key modulators in endometriosis pathogenesis is increasing of local production of estrogen (13). Many effects of sex steroids are mediated by their actions at their nuclear receptors, while growing evidences have shown that many of these effects may not be receptor dependent (14). Due to latency of disease diagnosis and occurred progression of the disease at the time of presentation at clinic, it is not possible to perform experiments with the aim of detection of predisposing factors, which are related to synthesis or play a role in sex steroid effects in endometriosis. Due to ethical considerations, controlled experiments such as disease progression monitoring by repeated laparoscopies are limited. Therefore, animal models of endometriosis can be the solution to perform extensive research on sex steroid effects and their related mechanisms of ectopic endometrial tissue or cells adherence, invasion and vascular establishment, development of new approaches for investigating the initial occurrence or recurrence prevention or even treatment of lesions.

Since now, the closest models to humans for the evaluation of endometriosis are non-human primates. Because of their high cost and handling limitation in the use of these models, small laboratory animals were used as alternative models of endometriosis. This literature review is aimed to provide comprehensive insight through hormone related animal models of endometriosis and compare different induction methods of endometriosis, advantages disadvantages, and their application for evaluation of sex steroid hormones effects in pathogenesis of endometriosis. Additionally, a summary of all published studies is provided and a novel scoring table is designed to attain a full acquaintance over most important aspects of available animal models.

2. Materials And Methods

We used PubMed/Medline database as the source for finding sex hormone related endometriosis researches. All included studies were published form 2010 to 2021. We used Mendeley Desktop application for screening the results and following search query was utilized in order to discover all related papers. Mentioned search query resulted 158 related papers in 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]).

3. Inclusion And Exclusion Strategies

We included studies that were published between 2010 to early 2021, which have proposed an endometriosis induction method in animals as the first criteria. An assessment of sex steroid hormones (SSH) or Hypothalamic pituitary gonadal (HPG) axis hormones had to be met (receptors or concentration assessment) as the second inclusion criteria. We reviewed all the studies that met our circumstances in section 4 and articles that represented a novel induction method were classified in segment 5 separately. The more popular older approaches that section 4 studies utilized were also reviewed and explained separately.

We considered sex hormones by terms of gonadal steroid hormones, testosterone, androgens, estradiol, estriol, estrone, estetrol, estrogens, phytoestrogens, progesterone, progestogen and progestins as SSH (15). Furthermore, luteinizing hormone (LH), follicle-stimulating hormone (FSH), Gonadotropin-releasing hormone (GnRH) and melatonin were considered as HPG hormones. We excluded non-English articles and review articles result. We also did not consider studies which have utilized steroid supplementation while inducing endometriosis in murine models of endometriosis as a hormone related study.

4. Hormone Based Endometriosis Studies Utilizing Previous Induction Methods

This section has included all the sex steroid hormone related studies of endometriosis and provides an insight through assessed therapeutics for endometriosis using animal models comprehensively. Additionally, section 4 provides targets of interest in endometriotic state, mechanisms and potential drugs which ameliorate the situation significantly. In the end of this section, a review of more frequently cited induction methods is prepared to provide a contrast between older methods and newer methods generally.

4.1. Sex steroid hormones related articles

4.1.1. Estrogen and its receptors role in endometriosis

The levels of estrogen, regulations of estrogen receptors (ERs) and involved pathways in endometriotic state is considerable. In this section, all related studies based on our inclusion criteria are presented and discussed separately to provide an overview over contribution of animal models to this field in a detailed way.

4.1.1.1. Puerarin and endometriosis

Blocking the effects of estrogen receptors can be used as a potent strategy for suppressing the lesion development. For instance, hER β al (estrogen β (Er β) agonists) and chemical estrogen blocker or modulator are used *in-vivo* and can be easily tested in this model. It is shown that puerarin, a phytoestrogen with a weak estrogenic effect, could suppress the endometriosis development in the rat model by binding to estrogen receptors. Puerarin was shown to ameliorate disease state by inhibition of P450arom expression while having no effects on estradiol receptor- α expression. These resulted reduced serum estrogen levels as well as reduced endometriotic tissue weight (16).

4.1.1.2. Xenografting of human tissue supplemented with estrogen and progesterone

Coudyzer et al. proposed an endometriosis model of mice in order to study self-renewal of endometrial tissue after menstruation. They subjected mice to human endometrial functionalis fragments grafting and supplemented them with of 17 β -estradiol and progesterone pellets for 21 days. Four days after removal of pellets, 17 β -estradiol pellets were utilized again to resemble early proliferative phase. They assessed estrogen receptor ER- α expression in the graft and noticed that the majority of cells in the stroma and glands were immunolabeled positively. They also noticed that hormone withdrawal led to rapid apoptosis and decrease in graft volume. The interesting finding was resistance of the graft volume to grow after reinsertion of estradiol pellet, despite detecting mitosis in the target tissue. (17).

4.1.1.3. Cisplatin and letrozole effect on rat model of endometriosis

Cisplatin (Cis-Diaminedichloroplatinum, CDDP) is the preferred drug in the treatment of endometriotic adenocarcinoma cancers (18). CDDP's anti-neoplastic activity comes from its binding ability to DNA molecules in target cells to induce DNA cross-links (18). These findings have made this drug a recommendable treatment for endometriosis (19).

It has been shown that Aromatase's enzyme is aberrantly expressed in ectopic and eutopic tissue in patients suffering from endometriosis (20). Considering that letrozole is an aromatase inhibitor which can suppress local and systematical estrogen production (21), it is hypothesized this drug could be probably used for treatment of endometriosis. In order to address that, a rat model of endometriosis was proposed. Cisplatin and letrozole both showed similar regression of the implants in the rat model while their effects on angiogenesis, protein expression and sex steroid hormones were not consistent (22).

4.1.1.4. Telocytes damage in endometriosis-affected rat oviduct and potential impact on fertility

Telocytes are widely available in various tissues of human body (23) and are also identified in endometrium tissue of rat (24). It has been revealed that telocytes population decline in women with endometriosis and tubal ectopic pregnancy (25). Auto-transplantation induction method was implemented to investigate telocytes morphology in rat model of endometriosis. Rats with endometriosis conditions shown to exhibit tissue degeneration, substantial decrease or loss of telocytes with elevated levels of inducible nitric oxide synthase (iNOS), Cyclooxygenase-2 (COX-2), lipid peroxide (LPO) and estradiol, as an inflammation indicators (26).

4.1.1.5. Niclosamide and endometriosis

It is documented that niclosamide disrupts multiple signaling pathways of STAT3 signaling in a variety of cancer models (27). Niclosamide could reduce the size of endometriotic implants in a mouse model of endometriosis by effecting inflammatory pathways. Niclosamide did not affect steroid hormone receptors in the endometriotic implants either, indicating that the drug does not disrupt ovarian function (28).

4.1.1.6. Neuroangiogenesis and endometriosis

Ectopic endometrial tissues have been revealed to contain nerve fibers in addition to excessive formation of blood vessels (29). Co-existence of nerve and vessel leads to known common chronic pain of endometriosis. Neuroangiogenesis is also known to be adjusted by axonal guidance proteins like SLIT (30). Greaves et al. showed that mRNA expression encoded by SLIT3 gene was significantly higher in ectopic endometrial tissue than normal peritoneum, suggesting probable SLIT3 role in vessel-nerve cell interaction. Additionally, they indicated that in response to activation of ER α , SLIT3 is secreted by neurons, increasing angiogenesis (31).

4.1.1.7. Macrophage-nerve cross talk and endometriosis

In a study by Greaves et al. a role for Estradiol in stimulating macrophage-nerve interactions using *in-vitro* and *in-vivo* models was demonstrated. They firstly showed macrophages and nerve fibers to be adjacent to peritoneal endometriosis lesions. Further, it was noted that ER β was expressed more than ER α in endometriosis local macrophages providing evidence that endometriosis can be considered as an estrogen-dependent neuroinflammatory disorder (32).

4.1.1.8. Simvastatin and endometriosis

Statins are shown to prohibit *in-vitro* proliferation of eutopic and ectopic endometrial stromal tissues (33) and can ameliorate endometriotic lesions in murine models (34). Simvastatin as a statin drug was evaluated by Taylor et al. in auto-transplantation baboon model of endometriosis. A daily dose of 20 mg simvastatin was shown to reduce various lesion size significantly. Additionally, estrogen receptors expression (Er1 and Er2) were evaluated. The treatment significantly suppressed the expression levels of ER2 in black lesions and upregulated the expression of ER1 in red lesions, supporting the suggestion that simvastatin could be effective by inhibition of mevalonate pathway, a growth reduction of endometrial lesions and ameliorating inflammation state. Furthermore, simvastatin significantly reduced the expression of neopterin, a marker of inflammation, oxidative stress, and immune system activation (35).

4.1.1.9. Chloroindazole (CLI), oxabicycloheptene sulfonate (OBHS) and endometriosis

CLI and OBHS are ER ligands with high selectivity for ER β and ER α respectively (36, 37). Zhao et al assessed the efficacy of these potent ligands for endometriosis treatment in α ERKO and α ERKO mice mouse models. They showed that CLI or OBHS could considerably reduce cell proliferation in ectopic lesion, vascularization and cyst formation and also ameliorate inflammation. There was no correlation between ER α deficiency an lesion growth, whilst ER β depletion in recipient animals caused reduction of ectopic lesions size (38).

4.1.2. Progesterone family and its receptor role in endometriosis

One of the specifications of endometriosis is progesterone resistance which was coined in 2000 by (39). There are multiple factors which support progesterone resistance like MicroRNAs (40), genetics (41), Mesenchymal stem cells (42), inflammation (43) and so on. The contribution of animal models to assess mechanisms underlying progesterone resistance and assessing the efficacy of potential drugs is presented in the following section:

4.1.2.1. Levonorgestrel loaded microspheres for the treatment of endometriosis

Levonorgestrel is a member of progestogen medications family which is utilized as a means of pregnancy control. Yuan et al. used microspheres loaded with levonorgestrel to target ectopic lesions in an endometriosis rabbit model and avoiding side effects while attaining more efficacy. The proposed drug delivery did not provoke any side effects, therefore it was proposed as an alternative therapy (44). In another study, intra-cystic injection of levonorgestrel-loaded polylactic acid microspheres in rat had long-term effectiveness via down-regulation of estrogen receptors in epithelium and stroma and Pr in the stroma of endometriotic tissues (45).

4.1.2.2. Nomegestrol acetate and endometriosis

Nomegestrol acetate is categorized as new progestins (46) and reveals a high selectivity for Pr (47) and shows anti-estrogenic profile on the endometrium (48). Zhang, Zhu, et al. benefited this principles and proposed a rat model of endometriosis in order to assess the potential efficacy. In order to amplify the results, they also used biodegradable microspheres as drug delivery approach to delay drug action. Treatment showed mitigation of ectopic lesions volume and decreased serum levels of progesterone, estradiol and Era while not effecting Pr expression level and vascular endometrial growth factor receptor 2 (49).

4.1.3. Multi hormone based studies and endometriosis

This sectioned was proposed to review estrogen and progesterone family related studies simultaneously. The utilization of animal models in revealing the effects of medications or pathophysiology of endometriosis is noticeable and all published studies are classified and presented as follows:

4.1.3.1. Dysregulations of steroid estrogen receptors and endometriosis

Estrogen receptors (50) and progesterone receptors (39) play a key role in development of endometriosis. Also G protein-coupled estrogen receptor 1 (gper1) are revealed to be upregulated in ectopic lesions. Mishra et al. utilized a mouse model of endometriosis to assess dysregulations of aforementioned receptors simultaneously. As a result, the level of ER α showed a reduction in expression while ER β was elevated in ectopic grafts. Gper1 and PR mRNA expression was decreased in a time specific manner (51).

4.1.3.2. Endometrial expression of steroidogenic factor 1 promotes cystic glandular morphogenesis

In a study by Vasquez et al. expression of steroidogenic factor 1 (SF1) subfamily in endometriosis was thoroughly investigated. This family is responsible for regulating the expression of the steroidogenic genes within the ovary. Considering the fact that the ovarian tissue is the main site of steroid synthesis via the conversion of cholesterol to estrogen, the levels of progesterone, estradiol in serum and the expression of sex hormone receptors such as Pgr and ER1 and fertilization status in a mouse model of endometriosis were evaluated. The study revealed that SF1 is directly related to the growth of ectopic endometrial lesion, absence of decidua response and infertility. So that expression of SF1 was followed by a decrease of PGR levels in the epithelial section of the graft but ESR1 levels was not affected. They also related the yielded infertility as a result of PGR dysregulation (52).

4.1.3.3. Niclosamide as a potential nonsteroidal therapy for endometriosis

Prather et al. evaluated the effect of niclosamide as an inhibitor of endometriosis progression by blocking NF- κ B, STAT3, and WNT signaling pathways. They further evaluated angiogenesis marker CD31, ER1 and PGR expression as well as the fertility status. Niclosamide could avoid implant growth considerably by decreasing cell proliferation. However, no significant differences of CD31 expression as well as fertility status were observed whereas epithelial and stromal ER1 and PGR expressions were not altered after administration of niclosamide indicating that it does not affect systemic estrogen function (Prather et al. 2016).

4.1.3.4. C-Jun NH2-terminal kinase (JNK) inhibitor (JNKI) bentamapimod and endometriosis

In parallel study with Palmer et al., (53) used a model of baboon endometriosis to assess whether JNKI solely or with medroxyprogesterone acetate (MPA) supplementation is effective for a more similar translational model to human. Treatment with JNKI solely and JNKI plus PMA, or cetrorelix resulted in decreased ectopic lesions. After treatments, FSH, LH and progesterone levels remained unchanged but estrogen levels were significantly changed (54).

4.1.3.5. High-fat diet (HFD) promotion of endometriosis in an immunocompetent mouse model

Polyunsaturated fatty acids (3-PUFA) levels influence immune, angiogenic, and proliferative factors implicated in the early establishment of endometriosis (55). High body mass index (BMI) is correlated with endometrial cancer occurrence (56) and high adiposity and

endometriosis are closely correlated (57). In a study, Heard et al. examined the effect of high-fat diet (45% fat kcal) on mouse model of endometriosis. Klf9 WT mice were used as recipients of endometrial fragments from Klf9 null mice (donors). They assessed the correlation thoroughly by using an immunocompetent mouse model of endometriosis. A high-fat diet favored number of endometriotic lesions, higher proliferation and lower apoptotic status and a difference in differ in steroid hormone receptor expression. So that HFD-fed recipients had lower levels of total Pr and Esr1 but no differences for Esr2 (58).

4.1.3.6. Extracellular matrix metalloproteinase inducer (EMMPRIN;BSG) expression in the baboon endometrium: Menstrual cycle and endometriosis

BSG is a glycoprotein which stimulates matrix metalloproteinase (MMP) production based on glycosylation and deglycosylation (59). It has been shown that MMPs like MMP1 and MMP2 are dysregulated in ectopic tissues while endometriosis happens (60, 61). For further investigations of other MMPs function, a baboon model is utilized for assessment of sex steroid hormones dysregulations in pathophysiology of endometriosis. They showed that exogenous estrogen and progesterone up-regulated expression of BSG and MMP and all MMPs except MMP-7 revealed significant dysregulation consequently (62).

4.1.3.7. A new isoform of steroid receptor coactivator-1 (SRC-1) and endometriosis

Nuclear receptor-mediated cellular processes are modulated by SRCs in a tissue-selective manner (63). The role of SRCs in progression of endometriosis was not disclosed before the following study. Han et al. proposed different platforms to study SRC-1 function. They used mice autotransplantation model, xenotransplantation of human biopsy from a patient in SRC-1^{-/-}:GFP-expressing mice and xenotransplantation of immortalized human endometrial epithelial cells (IHEECs) into ovariectomized Severe combined immunodeficiency (SCID) mice to evaluate SRC-1 function. SRC-1 proteolytic isoform was increased in ectopic tissue with surgically induced mice and in stromal cells biopsied from endometriosis patients as well. By using transgenic Tnf^{-/-} and Mmp9^{-/-} mice, they found that a novel axis of TNF- α /MMP9/SRC-1 isoform helps generating endometriosis. Contribution of animal modelling to this aspect of endometriosis progression is creditable (64).

4.1.3.8. Krüppel-like factor 9 (KLF9) deficiency and endometriosis

KLF9 is a member of Sp/KLF family (65) and its function is closely related to estrogen and Pr dysfunction and endometriosis (66). Heard et al. utilized mice endometriosis model and KLF9 null donors to evaluate hormonal response and signaling pathways. They showed that loss of KLF9 expression provokes endometriosis production and deregulation of Notch and Hedgehog signaling pathways in addition to steroid receptor-regulated pathways (67).

In another study by Heard et al., it was revealed that unlike KLF9, KLF13 gene was not statistically associated with lesion development and growth. Also transcription levels of Pgr and Esr1 were not altered despite showing reduction of total Pgr and Esr1 in immunohistochemistry (68).

4.1.3.9. Steroid sulfatase and endometriosis

Steroid sulfatase (STS) is an enzyme involved in estrogen biosynthesis and is expressed in endometrium ectopic tissues (69). Estrone-3-*O*-sulfamate (E2MATE) is irreversible STS inhibitor. Colette et al. used this principle to assess the potency of STS inhibitor as new therapy of endometriosis by using xenotransplanted mouse model of endometriosis. They showed that treatment of mice with E2MATE did not alter plasma estradiol levels, but inhibited STS activity in murine uterus, as well as in induced lesions. E2MATE reduced lesion weight and progesterone expression was increased after treatment in endometriotic tissues (70).

4.1.3.10. Cisplatin, letrozole and endometriosis

Reducing the estrogen secretion is investigated as a protocol for suppressing endometriosis progression using aromatase inhibitors. Aromatization of androgens into estrogens is done by aromatase enzymes. Letrozole is a third-generation aromatase inhibitor (71) and can be a potent drug for endometriosis treatment (72). In a rat model of endometriosis, letrozole induced apoptosis and decreased the volumes and histopathologic scores of the endometriotic foci through decreasing aromatase P450 and cyclooxygenase-2 expression (73). In addition, in rat auto-transplantation model, letrozole increased Bax expression and decreased Bcl-2 expressions as well as aromatase P450 and cyclooxygenase-2, which led to suppression of estrogen secretion (74). Cisplatin is one of the preferred drugs in the treatment of cancer (19). The relation of endometriosis and cancer has raised interests (75). In a study by Li et al. effects of cisplatin and letrozole on rat auto-transplantation model of endometriosis were assessed. The serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), testosterone (T), estradiol (E2) and progesterone (P) were assessed. The medication resulted in lower growth of implants,

lower vascular endothelial growth factor (VEGF), E2, P and higher levels of FSH, LH, and T levels in comparison to control group which is promising for probable treatment of endometriosis (22).

4.1.3.11. Bentamapimod induces regression of endometriotic lesions

In a study, Bentamapimod, a c-Jun N-terminal kinase inhibitor (JNKI) was assessed in xenotransplantation and Auto-transplantation model of endometriosis. Treatment of nude mice with Medroxyprogesterone acetate (MPA) did not ameliorate ectopic lesion but supplementation with Bentamapimod was shown to be significantly effective. Bentamapimod also improved immunity reactions, cytokines functionality. Progesterone resistance without disrupting estrogen related regulations (53).

4.1.3.12. Ferulic acid (FA), ligustrazine (LZ) and tetrahydropalmatine (THP) and endometriosis

FA, LZ and THP were proved to have ameliorating effects on endometriosis state (76). To understand the underlying mechanism of effects, Tang et al. proposed a rat model of endometriosis to benefit from. It resulted decreased levels of Estrogen, GnRH, FSH and LH and lower expression of ER as promising therapeutic effects (77).

4.1.3.13. Lipoxin A4 (LXA4) and endometriosis

Lipoxins are endogenous eicosanoids which have anti-inflammatory properties (78). Previous studies suggested a protective role of LXA4 in the development and progression of experimental endometriosis in mice (79). Due to lack of understanding of this protective mechanism, Kumar et al. used allotransplantation mouse model to reveal underlying mechanisms. They showed that LXA4 treatment significantly reduced ectopic lesion size and downregulated the pro-inflammatory cytokines and angiogenic factor. ER α expression was shown to be diminished by LXA4 and Pr was upregulated respectively (80).

4.2. Hypothalamic pituitary gonadal (HPG) axis hormones and its role in endometriosis

4.2.1. GnRH related endometriosis articles

4.2.1.1. SKI2670 and endometriosis

GnRH antagonists are preferred for endometriosis treatment due to instant suppression of gonadotropins and not revealing initial GnRH stimulation of GnRH agonists (81). In a study by Kim et al., antagonistic potential of SKI2670 in a monkey model was assessed. The treatment showed promising results in comparison to elagolix as a regular treatment as it lowered LH and FSH significantly (82).

4.2.2. Non-GnRH hormone related endometriosis articles

4.2.2.1. Melatonin and endometriosis

Some studies revealed that melatonin could decrease the volume of endometriotic foci in rat model of endometriosis (73, 83, 84). Although these studies indirectly showed the role of this axis in pathogenesis of endometriosis but further investigations using this animal models are necessary to explain the exact mechanisms of melatonin in endometriosis pathogenesis.

4.2.2.2. Human chorionic gonadotropin (HCG) and endometriosis

Wu et al. investigated efficacy of HCG as an option for endometriosis cure by using Auto-transplantation rat model. Shrinkage of endometriotic lesions have been shown in comparison to initial size. It was revealed that HCG ameliorated endometriosis state by reversing leptin upregulation in endometriotic tissues (85).

4.3. Frequently used methods

Among section 4 studies, some studies used an approach multiple times. We reviewed them briefly below:

the most popular approach is the well-known rat autotransplantation model from (86). The method is developed based on Sprague-Dawley rats that their slice of uterine were ablated and transplanted to their peritoneal cavity. Eight studies designed their studies based on this

model untouched or with minor changes which is outstanding after 30+ years.

The other approach from (87) is based on syngeneic or autotransplantation of uterine tissues from C57BL/6 mice. Two assessed studies have referenced this method as their method of choice. The study was meant to standardize the endometriosis animal modelling for future studies. They showed that orientation of grafted uterine tissue affects growth of ectopic lesions so that the optimal size for transplantation was 2 mm and perimetrium (outer serous layer of the uterus) with underlying myometrium showed higher growth. The interesting point was that syngeneic or autotransplantation showed identical growth rate.

In 1995, (88) tested the Sampson theory of retrograde menstruation by using baboon models (*Papio cynocephalus* and *Papio anubis*). They concluded that intraperitoneal injection of menstrual endometrium was more successful in generating ectopic lesions than luteal endometrium or by retroperitoneal injection means.

Two other studies referenced the method provided from (89). In this model, wild-type C57BL/6 mice as donor and recipient were used. The mice were in diestrous stage when their uterine were removed and divided into 3mm pieces. After autotransplantation, it took 14 days for recipient mice to reveal the fluid filled cysts. As said above, usage of 2mm pieces would be more ideal for generating ectopic lesions and standardizing the results in some way.

The method by (90) involves using allotransplantation C57BL/6 mice model of endometriosis and doing procedures for 40 days to obtain the final ectopic lesions. Initially menstruation was induced in mice. So that ovariectomized mice were firstly treated with estradiol-17 β and then treated with progesterone and sesame oil to induce decidualization. After progesterone withdrawal in 19th day of procedure, the shed endometrium tissue was collected and injected to donor mice intraperitoneally. Eventually, the recipient mice were sacrificed and the desired ectopic lesions were harvested for assessment. This model also supports the Sampson theory but needs an extensive time and labor to induce.

Another potent translational animal model of endometriosis was introduced by (91). The model was intended to make the process of distinguishing the ectopic lesions from eutopic tissue in donor mice more approachable. In this approach, they used enhanced GFP with C57/B6 background as donor and C57/B6 as recipient mice. So that after the procedure, the lesions were easily distinguishable under florescent microscopy and more intense in estradiol supplemented recipient mice. This model provides a reliable platform to study histological assessment of endometriotic tissue more precisely.

5. 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 1.) represents a modified combination of previous proposed scoring models to enhance the prediction of drug assessment while utilizing animal models. These studies are categorized as follows (Figure 1).

5.1. Auto-transplantation models of endometriosis related to SSH and HPG hormones

5.1.1. Steroidogenic factor 1 and endometriosis

Expression of the steroidogenic genes in the ovary is adjusted by steroidogenic factor 1 (SF1) (92). Endometriosis status is reported to be correlated with demethylation of SF1 promoter, leading to the excessive expression of the gene (93). Vasquez et al. utilized an auto-transplantation mouse model with activation of SF1 by Cre recombinase system ($Pgr^{cre/-}$ SF1^{LSL/-}). They showed generation of enlarged endometrial glands and downregulation of stroma *Esr1* and epithelial *Pr* as a result of SF1 expression. Auto-transplantation of uterine tissue was followed by an increase in size of ectopic lesions in SF1 activated mouse, leading to the deficiency in decidualization process and contributing to the infertility. Serum concentrations of progesterone and estradiol after gonadotropin stimulation were not altered significantly and similar results were noted for uterine and ovarian estradiol levels. They concluded that ovarian tissues of SF1 expressing mouse are in normal state and SF1 expression favors endometriotic lesion establishment which can be considered for future endometriosis model establishment (52).

5.1.2. Estrogen receptor β and endometriosis

The role of ER β in endometriosis progression was investigated in autotransplantation and xenotransplantation mouse by Han et al thoroughly. They showed an upregulation of ER β levels in mouse endometriotic tissues with enhancement of ER β activity, which resembles human status. They exploited mutant mice strains like to show ER β loss and gain of function effects too. They claimed that gain of ER β

function (ER β ^{-/-} mice) triggered ectopic lesion growth significantly. They also demonstrated that elevation of ER β functionality avoids TNF- α induced apoptosis and boosts proliferation, invasion, and adhesion activities of immortalized human endometriotic epithelial cells in (SCID) mice which can be considered as a suitable xenotransplantation model of endometriosis (94).

5.1.3. Activated AKT pathway promotes establishment of endometriosis

Decreased levels of steroid hormones in endometriosis state can be suggested as a risk factor for granulosa cell tumor detection where expression of AKT is upregulated (95). To demonstrate the role of AKT in endometriosis, autologous implantation PR^{Cre/+}PTEN^{f/+} mice were used by Kim et al. PTEN (phosphatase and tensin homologue deleted from chromosome 10) is regulatory gene which gets disrupted in the state of cancers (96). They showed that deletion of PTEN increased activation of AKT and decreased levels of Pr in the grafts respectively. They also used MK-2206 as an AKT inhibitor, it showed efficacy by increasing Pr in mouse ectopic tissue and decreasing viability of endometriotic tissue derived cells in vitro. (97).

5.2. Xenotransplantation models of endometriosis related to SSH and HPG hormones

5.2.1. Immortalized human eutopic endometrial stromal cells line for endometriosis studies

Primary endometrial cells are being preferred extensively for investigation of endometriosis. However, dedifferentiation of cells during culturing, losing hormone and cytokine responsiveness, life shortage, and the change of migration and invasion are the main objections for primary cells. Immortalized primary cell line derived from endometrial stromal cells were utilized from different species (98–100). In a study by Huang et al., initially, eutopic endometrial stromal cells were isolated from a 26-year-old patient suffering from endometriosis. After histological confirmation cells were infected by lentivirus containing Human telomerase reverse transcriptase (hTERT) to produce immortalized cell line (iheESCs) (101).

Cells revealed original morphology during continuous cell cultures, growth rate, mobility and estrogen/progesterone receptor expression. The decidualization of iheESCs was induced by progesterone and cAMP successfully. Cells proliferation was increased by estrogen and lipopolysaccharides (LPS) induced the IL-1 β and IL-6 promoting inflammatory response similar to the human endometriotic lesion derived cells. Moreover, no tumorigenicity was observed following injection of cells into BALB/c nude mice suggesting that this model would be ideal for future studies (101).

It is important to note that four previous studies (5.1.1, 5.1.2, 5.1.3, 5.2.1) did not consider proper life stages of animals to induce endometriosis. As we know, endometriosis is a disease which happens in reproductive age of women. To provide better translational results, we have to consider the life stages of animal to be adult too (102).

5.3. Allotransplantation models of endometriosis

5.3.1. Estrogen Receptor Signaling and endometriosis

ERs are proven to possess a key function in estrogen responsiveness (103). α ERKO and β ERKO mice which lack ER α and ER β respectively, were utilized as donor mice in order to assess the ER signaling pathway in recipient wild type mice model of endometriosis and vice versa as well. All grafts transplantations except the one from α ERKO to wild type mice responded with growth. They concluded that ectopic lesion development is mostly regulated by estradiol signaling via ER α than ER β , which can be considered, for future endometriosis modeling. Additionally, models generated in this study can be utilized for ER focused studies and receptor targeting treatments as well. (104). In another study by Burns et al., they utilized the same α ERKO and β ERKO mice strains as previous study to thoroughly assess initial stages of endometriosis induction. It was revealed that in endometriosis ectopic sites, white blood cells were seen disregard of ER α or estradiol in early stages of endometriosis. Additionally, inflammation and angiogenesis were observed. They suggested that endometriosis development can be categorized into two different phases: an immune-dependent phase and a hormone-dependent phase which should be considered for future studies based on hormonal or immunological approach (105).

5.3.2. Mouse model of ovarian endometriosis

In order to address the lack of a specific model to study ovarian endometriosis, Hayashi et al proposed a mouse model of endometriosis for the first time. So that uterus tissue from donor mice was minced and transplanted on ovaries of recipient mice donor mice. The model revealed ectopic lesion growth by four weeks and FSH receptor on the recipient mice were considerably decreased, suggesting fertility problems and CD10 immunopositivity as a marker of endometrial stromal cells outside the uterus (106).

5.3.3. A high mimicking mouse model of endometriosis

Using mouse models for endometriosis induction with intact immune system allows researchers to attain better understanding of inflammatory related responses (107). Greaves et al. proposed a mouse model of endometriosis using menstruation induced mouse model as donor mouse and unscathed mouse as recipient. The allotransplantation resulted higher expression of ER β in ectopic lesions and CD10 immuno-positivity. Also presence of local macrophage in lesions were suggested to contribute to inflammatory responses making this model an attractive choice to study endometriosis related immunologic responses (90).

5.3.4. Bazedoxifene and endometriosis

It has been shown that bazedoxifene as a third-generation selective estradiol receptor modulator, could reduce the size of endometriosis lesions in mice models of endometriosis (108, 109). Following bazedoxifene administration in mice, a decrease in expression levels of estrogen receptor mRNA was reported whereas no alteration in expression of Pr mRNA were seen (109).

The selected animal model in these studies was developed based on CD-1 mice. CD-1 mice stock uterine horns were grafted to peritoneum of recipient CD-1 mice to develop endometriosis model and assess Bazedoxifene efficacy in ectopic lesion suppression. The model selection attracts criticism due to selection of mouse stock. CD-1 mice are heterogeneous stock of mice, which are unable to provide the precision and accuracy of results due to undefined genetic variations. The usage of outbred strains for animal modeling is not suggested generally due to ability of accomplishing the same results with much smaller sample size using inbred stocks (110).

5.4. Spontaneous endometriosis

5.4.1. Spontaneous endometriosis in a Mandrill

Estrogen, progesterone receptors and the CD10 marker are the potential markers of human ectopic endometrial tissues (111, 112). Nakamura et al. used these parameters for confirmation of endometriosis existence in a dead mandrill (*Mandrillus sphinx*) exhibiting haemoperitoneum, petechiae and peritoneal ecchymoses. They noted eutopic and ectopic endometrial stromal cells in uterus and stromal-like cells outside the uterus, expressed Pr and CD10 markers. Also normal endometrial glands and the epithelium of the ectopic glands expressed estrogen receptor (113).

5.4.2. Spontaneous endometriosis in a rhesus macaque

Assaf and Miller examined a rhesus macaque (*Macaca mulatta*) which showed difficulty with breathing and weight loss. Their findings confirmed the existence of abdominal endometriosis by powerful expressing of Pr in ectopic lesions accompanied by a slight presence of estrogen receptor (114).

5.4.3. Endometriosis induced by unopposed estrogenicity

Nair et al. induced spontaneous endometriosis in baboon by an unopposed estrogenicity approach utilizing Pr antagonist (EC304). Initially they evaluated the role of progesterone in attachment of human endometrial stromal cells in vitro. Progesterone treatment significantly increased the rate of attachment of menstrual endometrial stromal cells peritoneal mesothelium (LP9) and increased rate of invasion. Therefore, they supplemented EC304 with progesterone treatment, which lead to multifocal stacks of differentiated endometrial glands and stroma on the surface of the uterus and peritoneal cavity. Administration of EC304 and progesterone clearly increased the expression of ER α as the direct hallmark of estrogenicity in the endometrial tissue (115).

Figure 1.

Infographic of novel endometriosis induction methods

6. Conclusion

Utilizing novel animal models to assess endometriosis pathophysiology is not something new (86, 116). There has been extensive research using proposed animal models to assess etiology (117), diagnosis (118), resemblance (119), genetics (120), biomarkers (121) and therapeutics (122) for endometriosis disease. Sometimes these studies have reported promising results to encounter endometriosis as a multifactorial gynecological disease (123).

However, the need for handling this uncomfortable situation is still concerned. For example, despite many efforts, researchers could not propose noninvasive, definite and reliable approaches to diagnose endometriosis yet (124). Therefore, women with probable endometriosis existence still have to deal with pain and side effects of invasive procedure such as laparoscopy woefully.

There is a vast contribution of animal models to this disease in order to eliminate these difficulties. Due to lack of data, major trustworthy reviews like systematic reviews or meta-analysis were unable to address these issues (125). So it is required to look back and revise preclinical procedures like animal modeling to provide more authentic data by enhancing research qualities.

This review has provided new insight through the relation of hormones and endometriosis by gathering recent published data and analyzing it meticulously. The proposed scoring system is designed to compare novel animal models that are proposed through the past decade.

6.1 Scoring table rationale and evaluation

We used scoring tables for model assessment which was inspired from (126-128). We also utilized proven hormonal markers (*ESR1*, *PGR*, *CYP17A1*) and other genetic markers (*BDNF*, *AGTR1*, *CCL2*, *C3*, *CD40*, *TIMP2*, *SERPINE1*, *CYP17A1*, *IGF1*, *IGF2*, *IL10*, *MMP1*, *MMP7* and *MMP9*) from study by (129) study to evaluate the models. The scoring was designed in a way that a contrast between 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 human physiologically and pathologically: (Non-human primate = 2, Non-human mammal = 1)

2. Spontaneous disease occurrence which is exclusive for Non-human primates gained highest scores, xenotransplantation models gained higher scores in comparison to autotransplantation / allotransplantation models due to utilizing cells or tissues from human which can be perceived as more closer to human pathological state:

(Spontaneous disease occurrence = 3, xenotransplantation = 2, autotransplantation / allotransplantation = 1)

3. Consistent pharmacological effects with humans by available verified drugs can be promising criteria 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 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 be in compliance with human photogenic state. The more similar the dysregulation, the better translational animal model would be:

(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)

6. There are also numerous genes which get disrupted in the state of endometriosis. gene regulations can be consistent with human body dysregulations or not:

(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)

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 diagnosis of the disease:

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

This table also provides novel insight for future studies to choose the most suitable model. It is worth mentioning despite achieving less score for non-human mammals in comparison to non-human primates, they benefit from wide availability, easy handling, cost effectiveness, faster growth and breeding. In non-human mammals segment, study by (130, 131) and (90) gained the highest score by providing key elements and resemblance to human endometriosis. (90) proposed their model in non-immunocompromised mice, which can be considered as an advantage for studies involving immunologic topics. While in humans endometriosis is an issue with adult women,

most of other studies in this category neglected utilizing adult animals (102). This simple selection can produce inaccurate results for clinical trials and major analyzes. In spite of providing a considerable approach for xenotransplantation, (101) did not provide adequate animal modelling assessment. Although, the mouse model by (108, 109) gained a considerable grade, it is not recommended to use the outbred stock (CD-1) due to genetic variation and suitable availability of other inbred mice strains.

Transgenic animals for endometriosis studies are gaining increasing attention for further investigation of the disease. Some of this transgenic mice exhibit endometriosis features, while the others just facilitate the investigation of the disease and induction of endometriotic state is done by utilizing the previous developed methods. Transgenic animal models in this field can be one of the most promising tools to examine functions of various genes precisely.

Non-human primates are considered to be very similar to humans genetically and physiologically. In addition, they are able to develop spontaneous endometriosis, which can be a positive factor in research terms. In addition to similarities to human, endometriosis is confirmed more accurately considering hormonal assessment; therefore, they achieved higher scoring results. In this segment, (115) has proposed the best model scoring wise. Unlike other models of non-human primates, this model utilized anti progestin to develop endometriotic lesions in baboons. Therefore, can be proposed as best available animal model for hormone related endometriosis assessment.

7. Abbreviations

Sex steroid hormones: SSH

Hypothalamic pituitary gonadal axis: HPG axis

Luteinizing hormone: LH

Follicle-stimulating hormone: FSH

Gonadotropin-releasing hormone: GnRH

Estrogen receptors: ERs

Progesterone receptors: PRs

G protein-coupled estrogen receptor 1: GPER1

Steroidogenic factor 1: SF1

High-fat diet: HFD

Matrix metalloproteinase: MMP

Extracellular matrix metalloproteinase inducer: BSG

Steroid receptor coactivator-1: SRC-1

Immortalized human endometrial epithelial cells: IHEECs

Severe combined immunodeficiency: SCID

Steroid sulfatase: STS

Estradiol: E2

Progesterone: P

Vascular endothelial growth factor: VEGF

Testosterone: T

Lipoxin A4: LXA4

8. Declarations

8.1. Ethics approval and consent to participate

Not applicable.

8.2. Consent for publication

Not applicable.

8.3. Availability of data and materials

Not applicable.

8.4. Competing interests

Authors have declared no conflict of interests.

8.5. Funding

No funding was received for this study.

8.6. Authors' contributions

A. T., A. S., and M. M. conceived and designed the format of the manuscript. A. S. and A. Z. collected the data, and drafted and edited the manuscript. A. T., A. S., A. Z., and M. M. drew the Figures and Tables. All the 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.

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Tables

Table 1
Comparison of new proposed methods of endometriosis induction for hormone related studies

	Species	Induction method	pharmacological effects	Relevant life stage	Hormonal evaluation	Genetic evaluation	Histological evaluation	Total	Reference
Optimal animal model	2	3	1	1	2	2	1	12	
5.1.1. Steroidogenic factor 1 and endometriosis	1	1	0	-1 (6–8 weeks old)	0	0	1	2	(52)
5.1.2. Estrogen receptor β and endometriosis	1	1	0	-1 (5 weeks old)	1	0	1	3	(94)
5.1.3. Activated AKT pathway promotes establishment of endometriosis	1	1	1	-1 (6 weeks old)	1	0	1	4	(97)
5.2.1. Immortalized human eutopic endometrial stromal cells line for endometriosis study	1	2	0	-1 (5-8 weeks old)	0	0	0	2	(101)
5.3.1. Estrogen Receptor Signaling and endometriosis	1	1	0	1 (Adult)	2	1	1	7	(104) (105)
5.3.2. Mouse model of ovarian endometriosis	1	1	0	1 (9 weeks old)	1	1	1	6	(106)
5.3.3. A high mimicking mouse model of endometriosis	1	1	0	1 (11 weeks old)	2	1	1	7	(90)

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

Relevant life stage: Identical life stage = +1, Not mentioned = 0, Non-identical life stage = -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

	Species	Induction method	pharmacological effects	Relevant life stage	Hormonal evaluation	Genetic evaluation	Histological evaluation	Total	Reference
5.4.1. Spontaneous endometriosis in a Mandrill	2	3	1	1 (Adult)	0	0	1	8	(132)
5.4.2. Spontaneous endometriosis in an Rhesus Macaque	2	3	1	1 (Adult)	0	0	1	8	(114)
5.4.3. Endometriosis induced by unopposed estrogenicity	2	3	1	1 (6-10 year old)	2	0	1	10	(115)
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									
Relevant life stage: Identical life stage = +1, Not mentioned = 0, Non-identical life stage = -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									

Note: Table 1 can be placed at the end of section 5.

Table 2
Non-novel animal models used by published studies in section 4.

#	Study section and number	Reference	Source of utilized method
1	4.1.1.1. Puerarin and endometriosis	(16)	(133)
2	4.1.1.2. Xenografting of human tissue supplemented with estrogen and progesterone	(17)	(134)
3	4.1.1.3. Cisplatin and letrozole effect on rat model of endometriosis	(22)	(87)
4	4.1.1.4. Telocytes damage in endometriosis-affected rat oviduct and potential impact on fertility	(26)	(86, 135)
5	4.1.1.5. Niclosamide and endometriosis	(28)	(89)*
6	4.1.1.6. Neuroangiogenesis and endometriosis	(31)	(90)
7	4.1.1.7. Macrophage-nerve cross talk and endometriosis	(32)	(90)
8	4.1.1.8. Simvastatin and endometriosis	(35)	(88)!
9	4.1.1.9. Chloroindazole (CLI), oxabicycloheptene sulfonate (OBHS) and endometriosis	(38)	(108, 136)
10	4.1.2.1. Levonorgestrel loaded microspheres for the treatment of endometriosis	(45)	(86)
11	4.2.2. Non-GnRH hormone related endometriosis articles	(49)	(86)
12	4.1.3.1. Dysregulations of steroid estrogen receptors and endometriosis	(51)	(137)
13	4.1.3.2. Endometrial expression of steroidogenic factor 1 promotes cystic glandular morphogenesis	(52)	(64)*
14	4.1.3.3. Niclosamide as a potential nonsteroidal therapy for endometriosis	(Prather et al. 2016)	(89)
15	4.1.3.4. C-Jun NH2-terminal kinase (JNK) inhibitor (JNKI) bentamapimod and endometriosis	(54)	(138)
16	4.1.3.5. High-fat diet promotion of endometriosis in an immunocompetent mouse model	(58)	(91)!
17	4.1.3.6. Extracellular matrix metalloproteinase inducer expression in the baboon endometrium: Menstrual cycle and endometriosis	(62)	(88, 139)
18	4.1.3.7. A new isoform of steroid receptor coactivator-1 is crucial for pathogenic progression of endometriosis	(64)	(140)
19	4.1.3.8. Krüppel-like factor 9 (KLF9) deficiency and endometriosis	(68)	(91)!
20	4.1.3.9. Steroid sulfatase and endometriosis	(70)	(141)
21	4.1.3.10. Cisplatin, letrozole and endometriosis	(22)	(87)
22	4.1.3.11. Bentamapimod induces regression of endometriotic lesions	(53)	(88)!
23	4.1.3.12. Ferulic acid (FA), ligustrazine (LZ) and tetrahydropalmatine (THP) and endometriosis	(77)	(86)
24	4.1.3.13. Lipoxin A4 (LXA4) and endometriosis	(80)	(86)*
25	4.2.1.1. SKI2670 and endometriosis	(82)	(86)
26	4.2.2.1. Melatonin and endometriosis	(73, 83, 84)	(86, 142, 143), (73, 144), (86)
27	4.2.2.2. Human chorionic gonadotropin (HCG) and endometriosis	(85)	(145)
!: Instead of referenced method, we mentioned the source article which provided the utilized method.			
*: The assessed article has mentioned modification of the source method.			

Note: Table 2 can be placed at the end of section 4.

Figures

Figure 1

Infographic of novel endometriosis induction methods