established in 2016

MAS JOURNAL of Applied Sciences

ISSN 2757-5675

DOI: http://dx.doi.org/10.52520/masjaps.206

Review Article

Endometriosis: A Review of Systematic Reviews and Meta-Analysis

Mehmet YILMAZ[1*](Orcid ID: 0000-0002-9930-4156)
Siirt Universitesi, Faculty of Medicine, Obstetrics and Gynecology Department, Siirt
*Corresponding author: jindrmehmet@gmail.com

Received: 18.11.2021 **Accepted**: 20.12.2021

Abstract

Endometriosis is a common disease with typically delayed diagnosis. Its prevalence is high among adolescents with pelvic pain symptom. Deposits of tissue outside uterine cavity depend on oestrogen. Progestins and oral contraceptives are not successful 1/3 of symptomatic women worldwide. Pathogenesis of endometriosis is not well understood but immune system plays a role in its pathophysiology. The aetiology of endometriosis remains largely unknown. Here in this review, reader may find a review of systematic reviews and meta-analysis published after 2015 on endometriosis.

Keywords: Endometriosis, systematic review, meta-analysis

1. INTRODUCTION

Endometriosis is a common disease affective on 5–10% of reproductive aged women globally. Its diagnosis is generally delayed for years, misdiagnosis is frequent, and effective therapy delivery is prolonged. Identification and treatment of endometriosis are necessary and can be facilitated by correct diagnosis. Endometriosis was defined as a chronic gynaecological disease with endometrial-like tissue outside the uterus and was thought to arise via retrograde menstruation. However, this description is not valid now and does not reflect true scope of the disease. It is clinically varied, heterogeneous pelvic lesions are present, and appearance of the disease outside reproductive tract is not well understood. Endometriosis is now considered a systemic disease rather than a disease predominantly affecting the pelvis. Endometriosis changes metabolism in liver and adipose tissue, causes systemic inflammation, and alters gene expression in the brain that causes pain sensitisation and mood disorders. The full effect of the disease goes beyond the pelvis. Recognition of the full scope of the disease will accelerate clinical diagnosis and allow for more comprehensive treatment (Taylor et al., 2021).

Endometriosis makes pelvic pain in adolescents with menstrual symptoms, affect activity, social and education life. Its prevalence among adolescents is high with pelvic pain symptoms. Endometriosis is treatable diseases and its recognition will ensure that patients are delivered earlier to appropriate specialists (Hirsch et al., 2020). Adolescent women with this disease are at increased risks as a result of frequent diagnostic delays, which in turn can exacerbate pain. Endometriosis research and treatment guidelines for adolescents are largely based on studies for adults and limited number of studies focuse on adolescents (Sieberg et al., 2020).

Deposits of endometrial tissue outside the uterine cavity depend on oestrogen and respond to the hormonal changes of the menstrual cycle. With no outlet, the resulting chronic inflammatory reaction may cause scarring, severe pain, adhesions, fatigue, subfertility and depression. Retrograde menstruation is believed as the main reason, but immunological failures and antibody production against endometrial cells may also play roles. Disesas has alike symptoms to adhesions, uterine fibroids, irritable bowel syndrome, recurrent urinary tract infections, pelvic inflammatory disease, and malignancy of the uterus, cervix, rectum, ovary or bladder, which makes diagnosis difficult. Conclusive diagnosis can be made only by laparoscopy, which is invasive and usually needs general anaesthetic. “Endometriosis UK Diagnosis Survey (2015)” determined that 50% of women wait for 4 or more years for diagnosis. Half of women surveyed visited family doctors minimum five times before get referred to specialist, and nearly 60% of women delayed seeking help as they guess the pain was normal. Prevalence was estimated to be up to 10% of women of reproductive age, and between 25% and 40% of women with subfertility, although without a simple screening test estimates are likely to be rough. “European Society of Human Reproduction and Embryology” guidelines on recommend endometriosis treatment with non-steroidal anti-inflammatory drugs, beside hormone therapies (combined oral contraceptive pill or progestogen, androgens, gonadotropin-releasing hormone analogues, or aromatase inhibitors). Surgical options cover excision or

ablation of endometriosis deposits, and hysterectomy (with oophorectomy) for women who have already had children and was not responded to conservative treatments. Patients with subfertility might also need specialised assisted reproductive technology (Thorley, 2015).

Progestins and reduced-dose oral contraceptives are not successful in 1/3 of symptomatic women worldwide, as a probably result of progesterone resistance. Oral gonadotropin-releasing hormone antagonists are effective therapeutic alternatives if first-line medication do not function. The development of gonadotropin-releasing hormone antagonists has resulted in oral drugs with fewer side-effects compared to other therapies and has allowed for rapid movement between treatments to optimise and personalise endometriosis care (Taylor et al., 2021).

Pathogenesis of endometriosis is not well understood but immune system has a role on pathophysiology. Elevated number of immune cells and changes in cell-mediated and humoral immunity were determined. Studies demonstrated that dendritic cells are susceptible to pro-endometriotic changes which may inhibit immature dendritic cells from maturation and induce immature dendritic cells into a macrophage phenotype. Additionally, growth and vascularization of endometriosis needs the presence of endogenous dendritic cell, which infiltrate endometriotic lesions and enhance endothelial cell migration via secretion of proangiogenic factors. But dendritic cell maturation suppresses this response, immature dendritic cells actively promote angiogenesis and growth, which leads to a shift in their immunologic role from presenting antigens to support angiogenesis and endometriosis progression (Laginha et al., 2022).

Systematic reviews and meta-analysis

Endometriosis-related fibrosis is a complex phenomenon with not clarified underlying mechanisms. Fibrosis is common in all forms and share classic endometriosis-related symptoms of pain and infertility. Studies published during last 23 years which examined fibrosis in superficial, ovarian, and deep infiltrating endometriosis was analysed by Vigano et al. (2020). Dominant cell types for the development of fibrosis were platelets, ectopic endometrial cells, macrophages, and sensory nerve fibers. Interactions of these cell types support the production of fibrosis through soluble factors, mainly transforming growth factor-β and other neuropeptides and cytokines. Cell types are critical on the pathophysiology of endometriosis and also contribute to fibrogenesis, thus supporting the theory that fibrosis is an inherent part of endometriosis.

Endometriosis presence may result with impaired ovarian reserve, while antral follicle count changes is controversial. A systematic analysis was conducted by Tian et al. (2021) which showed a significant reduction in antral follicle count and anti-Müllerian hormone and increase in serum Follicle-stimulating hormone concentrations in patients with endometriosis compared to controls. Antral follicle count for the ovary with endometrioma was also significantly lower than contralateral ovary of patients with unilateral ovarian endometriosis. Antral follicle count of endometriosis patients where ovaries were not affected (or at early stage) were similar to control group. As a result, endometriosis was associated with reduced antral follicle count and anti-Müllerian hormone and elevated serum concentrations of follicle-stimulating hormone. This was showing a decrease in ovarian reserve of endometriosis

patients, spesifically at ovarian endometrioma and advanced stage.

Impact of ovarian stimulation to the endometriosis progression or its recurrence was reviewed by Somigliana et al. (2019). As conclusions, 1) in vitro fertilization does not worsen endometriosis-related pain symptoms. 2) in vitro fertilization does not increase the risk of endometriosis recurrence. 3) impact of in vitro fertilization on ovarian endometriomas, if present at all, is mild. 4) intrauterine insemination can increase the risk of endometriosis recurrence. 5) deep invasive endometriosis may progress with ovarian stimulation. As overall conclusion, knowledge is generally reassuring (at least for in vitro fertilization) and does not justify aggressive clinical approaches such as prophylactic surgery before assisted reproductive technology treatment to prevent endometriosis progression or recurrence.

Current evidence suggests that endometriosis is a multi-causal and oestrogen-dependent diseases. Different epidemiologic studies explored relation between organochlorine chemicals and endometriosis. Meta-analysis revealed positive associations for dioxins, polychlorinated biphenyls and pesticides (Cano-Sancho et al., 2019).

Noventa et al. (2015) studied available evidences on ultrasound techniques in the management of deep pelvic endometriosis and compared their sensitivity and specificity to determine the most suitable site-specific method. Standard transvaginal sonography showed specificity bigger than 85% for all deep pelvic endometriosis sites, despite sensitivity ranging between 50% (vaginal wall, bladder, and rectovaginal septum) and 84% (rectosigmoid). Modified techniques such as bladder site tenderness–guided transvaginal sonography had a value of 97% for both sensitivity and specificity. Rectal endoscopy-sonography and rectal water contrast transvaginal sonography were both superior to transvaginal sonography in detecting rectosigmoid endometriosis with sensitivities and specificities over 92%. Concluded that transvaginal sonography should remain the first-line method in the evaluation of patients with suspicion of deep pelvic endometriosis. When transvaginal sonography is insufficient, second-line "modified-techniques" should be considered. Choosing the most effective technique is a challenge and should be based on patient history and clinical signs/symptoms.

Spontaneous hemoperitoneum in pregnancy, an nontraumatic intraperitoneal bleeding in pregnancy (up to 42 days postpartum), is related with serious adverse pregnancy outcomes. Lier et al. (2017) was conducted a systematic review and evaluated clinical results of spontaneous hemoperitoneum in pregnancy and their association with endometriosis. No association between the severity of spontaneous hemoperitoneum during pregnancy and the stage of endometriosis can be found. In most cases, spontaneous hemoperitoneum in pregnancy occurred at third trimester of pregnancy (30/59 cases; 51%); women presented (sub)acute abdominal pain (56/59 cases; 95%), hypovolemic shock (28/59 cases; 47%) and/or a decreased level of hemoglobin (37/59 cases; 63%). Signs of fetal distress were determined in 24/59 cases (41%). Imaging confirmed free peritoneal fluid in 37/59 cases (63%). During surgery, active bleeding happened in 51/56 cases (91%), originating from endometriotic implants (11/51 cases; 22%), ruptured utero-ovarian vessels (29/51 cases; 58%), hemorrhagic nodules of decidualized cells (1/51 cases; 2%) or a combination

(10/51 cases; 20%). Median amount of hemoperitoneum was 1600 mL (IQR 1.000mL–2.500 mL). From the 45/59 cases (76%) in which surgical interventions was carried out during pregnancy, 7/45 cases (16%) reported a successful continuation of pregnancy. 5/59 cases reported recurrence of spontaneous hemoperitoneum in pregnancy (recurrence rate 9%). The perinatal mortality rate was 27% (18/67 fetus), one maternal death was reported (1/59 cases). In conclusion, spontaneous hemoperitoneum in pregnancy is a very serious complication of pregnancy, highly associated with adverse pregnancy outcomes and particularly relevant to women with endometriosis. Currently preventive measures are lacking, therefore increasing the awareness and recognition is crucial to improve pregnancy outcomes.

2. Relation with other diseases

The potential link between endometriosis and Inflammatory Bowel Disease over the last two decades was investigated by Chiaffarino et al. (2020). Endometriosis shares with Inflammatory Bowel Disease features and symptoms so to become a significant diagnostic challenge, resulting in a delayed or indeterminate diagnosis. A positive association between endometriosis and Inflammatory Bowel Disease was reported.

Risk of extra-ovarian malignancies among women with endometriosis was studied by a survey on published articles by Gandini et al., (2019). They found an increased risk of endometrial and thyroid cancer, and inverse association with cervical cancer. No association was observed for breast cancer and melanoma.

Endometriosis prevalence may be underestimated due to difficulty in diagnosis Reproductive and anthropometric factors were associated with endometriosis risk. Women with endometriosis may have a higher risk for specific chronic diseases later in life. Characteristics robustly associated with a elevated risk for endometriosis including short menstrual cycle length, early age at menarche and lean body size, whereas greater parity has been associated with a lower risk. Relationships with other potential characteristics such as physical activity, dietary factors, and lactation have been less consistent (Shafrir et al., 2018).

3. Medical therapy

Studies in the last two decades on primary extrapelvic endometriosis were analysed by Andres et al. (2020). In patients with thoracic endometriosis involving the diaphragm, pleura, and lung, isolated and concomitant lesions occurred and favored the right side (80%). Patients with thoracic endometriosis presented with the triad of catamenial pain, pneumothorax, and hemoptysis. Thoracoscopy with resection followed by pleurodesis was the major procedure (29%). Adjuvant medical therapy with gonadotropin-releasing hormone was used in 1/7 of cases. Parietal endometriosis lesions involved primary lesions of the abdominal wall, perineum and groin. If present, symptoms include a palpable mass (99%), cyclic pain (71%) and cyclic bleeding (48%). Preoperative clinical suspicion was low, the use of tissue diagnosis was indeterminate (25%), and a few malignancies (8%) were suspected. Surgical treatment for parietal endometriosis included wide local excision (97%), with 5% recurrence and no complications.

Zakhari et al. (2020) analysed published studies to determine if dienogest therapy following endometriosis surgery reduces the endometriosis recurrence risk compared to expectant management. The incidence

rate of endometriosis recurrence in patients treated with dienogest was 2/100 women during average of 29 months follow-up versus 29/100 women expectantly managed over average of 36 months follow-up. The likelihood of recurrence was significantly reduced with postoperative dienogest. As a conclusion, patients receiving dienogest after conservative surgery for endometriosis was found to have significantly lower risk of postoperative disease recurrence than those who were expectantly managed.

Conventional endometriosis therapies mainly focus on decreasing estrogen systemic levels; but, without desirable effectiveness and with significant side effects. Interest is growing to the usage of herbal medicine for the treatment of endometriosis. Most of studies on herbal medicines in endometriosis were in vitro and animal and only three clinical trials found and included in the review of Bina et al., (2019). One of these studies was on *Pinus pinaster* bark extract (Pycnogenol) and two were on Chinese herbal formulas. The studies were on phytochemicals and mostly focused on polyphenolic compounds and sesquiterpenes. Molecular mechanisms of action involved: 1) Anti-inflammatory (via reduction of proinflammatory cytokines such as interleukins, transforming growth factor-beta, tumor necrosis factor-α, nuclear factor-kappa B, growth factors). 2) Antioxidant (through downregulation of hydrogen peroxide, malondialdehyde, reactive oxygen species and upregulation of superoxide dismutase). 3) Anti-proliferative and apoptotic (via enhancing Bcl-2-associated X protein/ B-cell lymphoma-2 and caspase3, 8 and 9 activity). 4) Anti-angiogenic (by downregulation of vascular endothelial growth factor receptors/vascular endothelial growth factor). 5) Anti-invasive (via decreasing expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and matrix metalloproteinases). 6) Immunomodulatory, and estrogen modulating activities. As a result, medicinal plants was found as a valuable source for identifying new drugs for treatment of endometriosis.

4. Pregnancy outcomes

Lantsberg et al. (2020) searched studies on fertility preservation techniques in the context of women with endometriosis and determined that a relative lack of evidence addressing the use of fertility preservation techniques in women with endometriosis. Women with endometriosis may benefit from fertility preservation techniques. However, there currently is a paucity of data in this population, especially when compared with other indications for fertility preservation.

Zullo et al. (2017) evaluated the effect of endometriosis on pregnancy outcomes. Women with or without endometriosis searched and analyzed 1.924.114 women. In most of them, the diagnosis of endometriosis was made histologically after surgery. Women with endometriosis had a statistically significantly higher risk of preterm birth, miscarriage, placenta previa, small for gestational age, and cesarean delivery compared with the healthy controls. No differences were found in the incidence of gestational hypertension and preeclampsia. As a conclusion, they determined that women with endometriosis have a statistically significantly higher risk of preterm birth, miscarriage, placenta previa, small for gestational age infants, and cesarean delivery.

5. CONCLUSIONS

Progestins and oral contraceptives are not successful 1/3 of symptomatic women worldwide. Pathogenesis of endometriosis is not well understood but immune system plays a role in its pathophysiology. The aetiology of endometriosis remains largely unknown.

Currently, there are no comparative studies to provide recommendations regarding optimal diagnostic methods, treatment options, and outcomes for endometriosis involving extrapelvic sites.

The potential effects on deep invasive endometriosis and the possible synergistic effect of stimulation and pregnancy are two areas that need to be explored further.

Given the complexity of endometriosis and lack of known biomarkers suitable for population-based research, carefully designed observational studies play an important role in better understanding the aetiology of endometriosis. Considering the high economic and societal cost associated with endometriosis, further research on this field is urged.

Adolescents with endometriosis are at a particular risk for pain due to diagnostic delays. A multidimensional research method is needed: Inflammation; Nerve, Brain; Psychology.

REFERENCES

Andres, M. P., Arcoverde, F. V., Souza, C. C., Fernandes, L. F. C., Abrão, M. S., Kho, R. M. 2020. Extrapelvic endometriosis: a systematic review. Journal of minimally invasive gynecology, 27(2): 373-389.

Bina, F., Soleymani, S., Toliat, T., Hajimahmoodi, M., Tabarrai, M., Abdollahi, M., Rahimi, R. 2019. Plant-derived medicines for treatment of endometriosis: a comprehensive review of molecular mechanisms. Pharmacological research, 139: 76-90.

Cano-Sancho, G., Ploteau, S., Matta, K., Adoamnei, E., Louis, G. B., Mendiola, J., Antignac, J. P. 2019. Human epidemiological evidence about the associations between exposure to organochlorine chemicals and endometriosis: Systematic review and meta-analysis. Environment international, 123: 209-223.

Chiaffarino, F., Cipriani, S., Ricci, E., Roncella, E., Mauri, P. A., Parazzini, F., Vercellini, P. 2020. Endometriosis and inflammatory bowel disease: A systematic review of the literature. European Journal of Obstetrics & Gynecology and Reproductive Biology, 252: 246-251.

Gandini, S., Lazzeroni, M., Peccatori, F. A., Bendinelli, B., Saieva, C., Palli, D., Caini, S. 2019. The risk of extra-ovarian malignancies among women with endometriosis: a systematic literature review and meta-analysis. Critical reviews in oncology/hematology, 134: 72-81.

Hirsch, M., Dhillon-Smith, R., Cutner, A., Yap, M., Creighton, S. M. 2020. The prevalence of endometriosis in adolescents with pelvic pain: a systematic review. Journal of Pediatric and Adolescent Gynecology.

Laginha, P. A., Arcoverde, F. V. L., Riccio, L. G. C., Andres, M. P., Abrão, M. S. 2022. The role of dendritic cells in endometriosis: A systematic review. Journal of Reproductive Immunology, 149: 103462.

Lantsberg, D., Fernando, S., Cohen, Y., Rombauts, L. 2020. The role of fertility preservation in women with endometriosis: a systematic review. Journal of minimally invasive gynecology, 27(2): 362-372.

Lier, M. C., Malik, R. F., Ket, J. C., Lambalk, C. B., Brosens, I. A., Mijatovic, V. 2017. Spontaneous hemoperitoneum in pregnancy (SHiP) and endometriosis—a systematic review of the recent literature. European Journal of Obstetrics & Gynecology and Reproductive Biology, 219: 57-65.

Noventa, M., Saccardi, C., Litta, P., Vitagliano, A., D'Antona, D., Abdulrahim, B., Gizzo, S. 2015. Ultrasound techniques in the diagnosis of deep pelvic endometriosis: algorithm based on a systematic review and meta-analysis. Fertility and sterility, 104(2): 366-383.

Shafrir, A. L., Farland, L. V., Shah, D. K., Harris, H. R., Kvaskoff, M., Zondervan, K., Missmer, S.A. 2018. Risk for and consequences of endometriosis: a critical epidemiologic review. Best practice & research Clinical obstetrics & gynaecology, 51: 1-15.

Sieberg, C. B., Lunde, C. E., Borsook, D. 2020. Endometriosis and pain in the adolescent-striking early to limit suffering: A narrative review. Neuroscience & Biobehavioral Reviews, 108: 866-876.

Somigliana, E., Viganò, P., Benaglia, L., Busnelli, A., Paffoni, A., Vercellini, P. 2019. Ovarian stimulation and endometriosis progression or recurrence: a systematic review. Reproductive biomedicine online, 38(2): 185-194.

Taylor, H. S., Kotlyar, A. M., Flores, V. A. 2021. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. The Lancet, 397(10276): 839-852.

Thorley, J. 2015. Marching for endometriosis awareness. The Lancet Diabetes & Endocrinology, 3(6): 412.

Tian, Z., Zhang, Y., Zhang, C., Wang, Y., Zhu, H. L. 2021. Antral follicle count is reduced in the presence of endometriosis: a systematic review and meta-analysis. Reproductive BioMedicine Online, 42(1): 237-247.

Vigano, P., Ottolina, J., Bartiromo, L., Bonavina, G., Schimberni, M., Villanacci, R., Candiani, M. 2020. Cellular components contributing to fibrosis in endometriosis: A literature review. Journal of minimally invasive gynecology, 27(2): 287-295.

Zakhari, A., Edwards, D., Ryu, M., Matelski, J. J., Bougie, O., Murji, A. 2020. Dienogest and the risk of endometriosis recurrence following surgery: a systematic review and meta-analysis. Journal of Minimally Invasive Gynecology, 27(7): 1503-1510.

Zullo, F., Spagnolo, E., Saccone, G., Acunzo, M., Xodo, S., Ceccaroni, M., Berghella, V. 2017. Endometriosis and obstetrics complications: a systematic review and meta-analysis. Fertility and sterility, 108(4): 667-672.