



## ARTICLE

### A REVIEW OF ENDOMETRIOSIS: FOCUS ON ITS PATHOPHYSIOLOGY, QUALITY OF OOCYTE AND EMBRYO, AND THE MANAGEMENT OF INFERTILITY

Tita Yuningsih<sup>1\*</sup>, Arleni Bustami<sup>1</sup>

<sup>1</sup>Fakultas Kedokteran, Universitas Indonesia, Jakarta, Indonesia

\*Correspondence email : [tita\\_yuningsih@yahoo.com](mailto:tita_yuningsih@yahoo.com)

#### ABSTRACT

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial tissue/lesion outside the uterus. Unraveling the pathogenesis and pathophysiology of endometriosis remains an elusive target. Among various mechanistic theories, the menstrual retrograde theory is considered favorable for explaining endometriosis, which is corroborated by the presence of certain survival factors that allow the growth and persistence of endometrial cells. This review set out to provide an updated insight into the etiology, quality of oocytes and embryos, and management of infertility of women with endometriosis undergoing *in-vitro* fertilization (IVF) cycles. Database searches were conducted using PUBMED, employing keywords such as endometriosis, oocyte quality, and embryo quality. The menstrual retrograde theory is considered prominent for elucidating the pathophysiology of endometriosis. Given the chronic inflammation in the reproductive tract associated with endometriosis, there is evidence observing a negative impact on oocyte quality and endometrial receptivity that could lead to infertility. Account for about 10-40% of women with endometriosis are administered IVF programs to achieve pregnancy and deliver healthy babies. Through IVF, oocytes can be fertilized and cultured *in vitro*; thereby, avoiding unfavorable *in-vivo* environments of tubal and endometrium due to endometriosis. The severity of endometriosis determines the quality of oocyte, embryo, and clinical pregnancy outcomes attained through the IVF program.

**Keywords:** Endometriosis, Embryo Quality, In Vitro Fertilization, Oocyte Quality

#### АБСТРАКТ

Эндометриоз-это хроническое воспалительное заболевание, характеризующееся наличием эндометриальной ткани/лезиона за пределами матки. Разгадка патогенеза и патофизиологии эндометриоза остается труднодостижимой целью. Среди различных механистических теорий благоприятной для объяснения эндометриоза считается менструально-ретроградная теория, которая подтверждается наличием определенных факторов выживания, обеспечивающих рост и персистенцию клеток эндометрия. Цель данного обзора - дать обновленное представление об этиологии, качестве ооцитов и эмбрионов и лечении бесплодия у женщин с эндометриозом, проходящих циклы экстракорпорального оплодотворения (ЭКО). Поиск по базам данных проводился в PUBMED по таким ключевым словам, как эндометриоз, качество ооцитов и качество эмбрионов. Теория ретроградной менструации считается основной для выяснения патофизиологии эндометриоза. Учитывая хроническое воспаление в репродуктивном тракте, связанное с эндометриозом, есть данные, свидетельствующие о негативном влиянии на качество яйцеклеток и восприимчивость эндометрия, что может привести к бесплодию. Около 10-40% женщин с эндометриозом проходят программу ЭКО, чтобы достичь беременности и родить здорового ребенка. С помощью ЭКО ооциты могут быть оплодотворены и культивированы *in vitro*, что позволяет избежать неблагоприятных условий *in-vivo* для труб и эндометрия, вызванных эндометриозом. Тяжесть эндометриоза определяет качество ооцитов, эмбрионов и клинических исходов беременности, достигаемых в программе ЭКО.

**Ключевые слова:** эндометриоз, качество эмбрионов, экстракорпоральное оплодотворение, качество ооцитов

## INTRODUCTION

Currently, none of the currently available theories are sufficient to elucidate the pathophysiology of endometriosis exclusively. The complexity of this hormonal disease involves several factors including genetics, immunological aspects, and inflammation. The first proposed theory revolves around the “so-called” menstrual retrograde, which is favorable in deciphering the pathophysiology of endometriosis. Throughout the menstrual cycle, cellular components or fragments of endometrial tissue retrogradely move from the fallopian tube tract to the pelvic cavity, successfully evading immune cells and persisting in an uncommon location. As a consequence, this process could induce pro-inflammatory and neuroangiogenic responses.

The second theory suggests the concept of “metaplasia coelomic” presuming that coelomic cells, originally forming the Mullerian ductus and uterus, transform into different types of cells including endometrial cells. The third theory proposes that the remaining Mullerian cell lineage contributes to the formation of endometrial cells. The fourth theory describes lymphovascular metastasis suggesting migration of endometrial cells through blood vessels and the lymphatic system to form lesions in the pelvic area. The last theory proposes the contribution of genetics and epigenetics differences could be the underlying factors supporting other theories. Menstrual retrograde postulated by Sampson stands out prominently among other theories in elaborating the pathophysiology of endometriosis. Endometrial fragments present in the menstrual blood could be the origin of endometrial lesions on the surface of other organs or within the peritoneal cavity, thereby inducing inflammation and proangiogenic responses. Given that these endometrial fragments contain progenitor or stem cells, it has been suggested that two distinct types of progenitor cells may contribute to the formation of typical and atypical endometriosis. Typically, an endometrial lesion contains endometrial glandular cells surrounded by stromal cells. In contrast,

atypical endometriosis lesions only contain endometrial stromal cells.<sup>7</sup> In cases of endometriosis, the stromal cells of endometrium exhibit adhesive properties, a consequence of integrin alteration and localized inflammation response.<sup>2,7</sup> To persist outside the uterus, endometrial cells should be able to escape from apoptotic induction, adhere to the peritoneal cavity, induce extracellular matrix degradation, prompt the generation of new vascularization, exhibit steroidogenic capacity, and evade immune cell activity. Understanding how endometrial cells can construct a support system to survive and cultivate immunosuppressive mechanisms becomes particularly intriguing. Endometrial cell proliferation depends on estradiol levels, accessible either locally or systemically. The endometrial lesions are estimated to induce an increase in aromatase and acute steroidogenic regulatory protein, coupled with decreased 17 $\beta$ -hydroxysteroid dehydrogenase-2 expression. The presence of aromatase enzyme in endometrial lesions proves the steroidogenic activity of de novo estrogen synthesis. In addition, endometrial lesions were shown to express estrogen- $\beta$  receptor remarkably which serves to hinder apoptosis, reduce the expression of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ); and consequently facilitate lesion growth and persistence. The heightened expression of interleukin-1 $\beta$  escalates endometrial cell adhesion, proliferation, and mesenchymal-epithelial transition.<sup>2</sup>

Ectopic endometrial cells or tissue may induce localized inflammation and immune responses by producing cytokines, chemokines, and prostaglandins. Alterations in immune cell function are considered a pivotal factor contributing to inflammation. Despite compromised estrogen production, essential for the proliferation and persistence of endometrial lesions, immune system dysfunction remarkably influences endometrial lesions' persistence by impairing immune cell phagocytosis ability. It is estimated that menstrual retrograde occurs for about 90% of cases indicating the predominant function of peritoneal

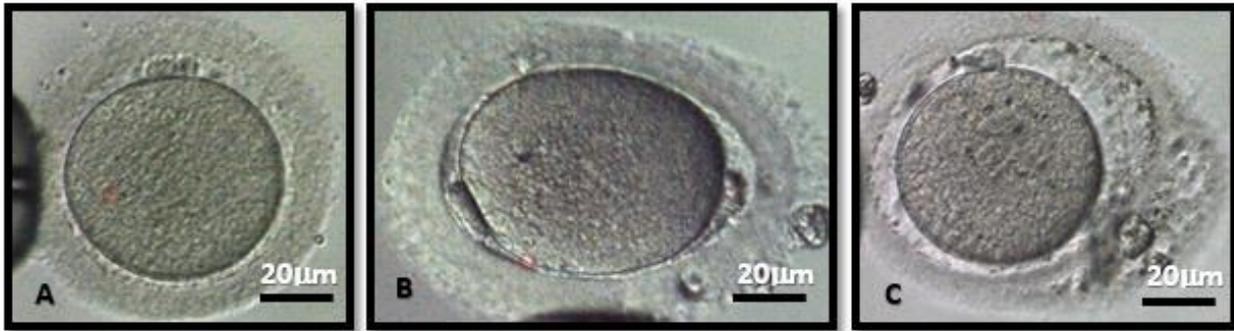
macrophages in effective clearance, with only 10-15% of the events eventually leading to endometriosis.<sup>8</sup>

In endometriosis, an observable increase in hyperactivated macrophages is noted within the peritoneal fluid, commonly characterized by the expression of surface marker CD25+. In addition to that, elevated production of monocyte chemoattractant protein 1, interleukin (IL)-1 $\alpha$ , tumor necrosis factor (TNF)-1 $\alpha$ , and IL-6 is apparent. Particularly noteworthy is the pivotal role of IL-1 in the regulation of inflammatory and immune cells, capable of inducing the secretion of other cytokines such as IL-2, and IL-8, regulated upon activation, normal T cell expressed and secreted (RANTES, macrophage migration inhibitory factor and prostaglandins).<sup>8</sup>

Impact on the quality of oocytes and embryos Oocyte quality. Endometriosis-induced inflammation could compromise folliculogenesis and ovulation. In aberrant peritoneal and follicular circumstances characterized by elevated cytokines production, growth factors, and vasoactive substances, there is a risk of damaging the oocyte's intrinsic integrity.<sup>9,10</sup> Moreover, the notable occurrence of somatic granulosa-cell apoptosis, which tightly encloses the oocytes, is observed leading to heightened risk of compromising essential nutrients and growth factors for follicular growth, maturation, and maintaining oocyte quality; hence, this compromised environment may give rise to oocytes with suboptimal or poor quality. Several studies have investigated the quality of oocytes obtained from endometriosis and compared that quality with non-endometriosis infertile women such as those with tubal problems. In a study conducted by Borges and Coworkers in 2015,<sup>11</sup> a significant increase in oocyte exhibiting extra-cytoplasmic abnormality was observed but not with the intra-cytoplasmic abnormalities (Figure 1). This was accompanied by reduced embryo quality as well as implantation rates. However, comparable outcomes were noticed in terms of the number of fertilized oocytes, number of a blastocyst, ongoing pregnancy, miscarriage,

and cycle cancellation rate when compared to those infertile women with tubal factors. In the case of endometrioma, notable observations include a low number of follicles with a diameter of  $\geq 16$  mm, suboptimal oocyte quality, and insufficient response to gonadotropin stimulation. A previous study proposed that the primary factor contributing to reduced implantation and clinical pregnancy in endometriosis is the poor quality of oocyte obtained.<sup>12</sup> Additionally, Rakhimberdievich and Colleagues observed maturation rate of both GV and MI oocytes *in vitro*. Their observation indicated that immature oocytes from women with endometrioma exhibited less *in-vitro* maturation capacity in comparison to the control group.<sup>13</sup> Contradictory results, however, were reported by Hamdan and Coworkers in a systematic review suggesting a similar quality of endometriosis-derived oocytes and non-endometriosis-derived oocytes in terms of oocyte morphology.<sup>14</sup>

Accurate oocyte quality assessment can be achieved by utilization of non-invasive growth factors biomarkers from the TGF $\beta$  family such as bone morphokinetic protein 15 (BMP-15) and growth differentiation factor (GDF-9) in either cumulus-granulosa cells or follicular fluid. Physiologically, these biomarkers play an essential role in granulosa cell proliferation and differentiation, ultimately supporting oocyte development. Increased expression of both BMP-15 and GDF-9 serves as an indicator of good-quality oocytes. In an effort to comprehensively understand the extent to which endometriosis could impede oocyte potential, two studies were conducted. However, none of these two biomarkers showed significant expression between endometriosis and the control group.<sup>15,16</sup> It was noted that confounding factors may have influenced these results. The study sample comprised women with endometriosis undergoing gonadotropin stimulation, potentially introducing intervention that could interfere with the expression of targeted biomarkers.



**Figure 1.** Oocyte morphology, (a) normal oocyte, (b) oocyte with extracellular deformity, (c) extra-cytoplasmic ZP abnormality.

Eventually, the utilization of oocyte donors from healthy women has been shown to enhance implantation, clinical pregnancy, and live birth rate in infertile women with endometriosis. Conversely, employing oocyte donors with endometriosis rarely results in pregnancy in infertile women without endometriosis, suggesting that poor oocyte quality may be the underlying factor contributing to infertility.<sup>18</sup>

#### Embryo quality

Observation revealed a reduced number of blastomeres in embryos generated from women with endometriosis. Also, there was an elevated incidence of developmentally arrested embryos compared to those generated from women without endometriosis. It has been hypothesized that immunological disturbance in peritoneal fluid as well as elevated free radical molecules in endometriosis, exert a detrimental impact on pre-implantation embryo development. Supporting the presumption, empirical evidence demonstrates that embryos derived from are prone to slower development than those embryos obtained from infertile women with tubal defects.<sup>19</sup>

Management of infertility treatment for endometriosis. The therapeutic approach for endometriosis depends on clinical symptoms such as cramping, pain, and infertility. Pain management often involves the use of contraception drugs. There is potential for pain recurrence in certain cases. On the other

hand, pregnancy has been observed to reduce endometrial pain symptoms. While medicinal therapy has proven effective for endometrial pain management, its impact on fertility treatment remains uncertain.

Concerning endometriosis-related infertility, treatment set out to improve the odds of conception through either a natural cycle or assisted reproductive technology. Fertility management approaches are suitable for young women diagnosed with mild or moderate endometriosis, whereas interventions including intra-uterine insemination and in-vitro fertilization should be considered for women with critical age of reproduction. In case of severe endometriosis, male infertility, tubal dysfunction, or a combination of both male and female infertility, immediate action to IVF is recommended.<sup>9</sup>

IVF is at the forefront of assisted reproductive technology against infertility. The successful birth of Louis Brown through the IVF program in 1978 has brought hope to treat infertile couples. The major indication for IVF for couples who have difficulty achieving natural pregnancy is due to both male and female fertility issues such as ovulatory dysfunction, impaired tubal function, idiopathic infertility, and endometriosis.<sup>1</sup> The IVF process comprises several crucial consecutive steps starting from ovarian stimulation, oocyte retrieval, fertilization, embryo culture, and embryo transfer. Monitoring the entire pre-implantation

process makes IVF particularly advantageous in addressing infertility due to endometriosis. IVF effectively mitigates the risk related to exposing gametes and embryos to unfavorable *in-vivo* environments due to endometriosis-related inflammation. According to recent 2017 data, over 300.000 babies were born through IVF programs with the projection foreseeing an increase due to the elevated infertile population worldwide. The clinical management of endometriosis through IVF presents a challenge, primarily relying on the ability of fertility specialists can select the most competent oocyte; thereby ensuring the obtained of good quality embryos.

Several randomized studies have demonstrated that the utilization of progestin and GnRH agonists did not improve fertility of both mild and moderate endometriosis. A cohort of 71 women with mild or moderate endometriosis receiving 6 months of GnRH agonist drug showed comparable clinical pregnancy rates to those without such administration. A systematic review and meta-analysis of 16 randomized studies revealed that the utilization of ovulation-suppressing drugs including medroksiprogesteron, gestrinone, oral combination pills, and agonist GnRH did not improve clinical pregnancy than those without drugs administration (OR 0.74; 95% CI 0.48 to 1.15) or even danazol (OR 1.3; 95% CI 0.97 to 1.76).<sup>1</sup>

## CONCLUSION

Endometriosis may adversely impact the *in-vivo* reproductive system, leading to potential complications in fertilization, embryo development, and implantation rate, ultimately contributing to the clinical manifestation of infertility. Disruptions in both anatomical and immunological aspects among women with endometriosis contribute to an unfavorable *in-vivo* environment. IVF recognized as the most effective ART treatment could be recommended with success rates depending on endometriosis severity.

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## DECLARATION

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