Pathomechanism of Infertility in Endometriosis

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1. Introduction

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction (Kennedy *et al.*, 2005). Infertility is one of clinical manifestation of endometriosis showed by the difference of fecundity. At our tertiary hosital pelvic endometriosis is frequently found in infertile women: 23,8 % (1987), 37,2 % (1993) and 50 % (2002) cases of diagnostic laparoscopy (Samsulhadi, 2002).

An association between endometriosis and infertility has repeatedly been reported in the literature, but an absolute cause-effect relationship has not yet been confirmed. The controversy regarding whether endometriosis is a cause of infertility or an incidental finding is ongoing (ASRM, 2006; Gupta *et al.*, 2008). Many theories of endometriosis which may impair fertility have been suggested during the years, and new hypotheses and approaches to the problem have arisen with the application of assisted reproduction techniques (Garrido *et al.*, 2002). Data on the impact of endometriosis on the results of in-vitro fertilization and embryo transfer (IVF-ET) treatment are not consistent. Several theories have been proposed to identify the pathomechanism of infertility in endometriosis. None of these theories can completely explain these association. Based on many reports the possible mechanisms that could cause infertility in endometriosis are pelvic adhesion and endometrioma and also excess production of inflammatory factors in micro environment that both play a role in alteration fertility function. Severe endometriosis is associated with pelvic adhesions leading to a possible mechanic or anatomic disturbance of fertility, in the other hand a mild stage may have a direct and indirect negative effect on folliculogenesis, oocyte development, sperm function, embryogenesis, and endometrium receptivity (Barnhart *et al.*, 2002). Our aim in the present review is to describe an update on several approaches of the pathomechanism of infertility in endometriosis, based on its impact on a number of pathologic conditions, such as: pelvic adhesion and endometrioma, abnormal folliculogenesis and impaired oocyte function, altered sperm function, reduced embryo quality, and impaired endometrium receptivity.

2. Pelvic adhesion and endometrioma

The mechanisms by which endometriosis impairs fertility have not been completely determined but are likely varied. Ovarian involvement and adhesion that block tubal motility and pick-up of the egg could be a main causative of mechanical interference on

fertility especially in severe endometriosis due to a possible mechanic or anatomic disturbance such as extensive pelvic adhesions. Pelvic endometriosis, the most common form of the disease, could be associated with increased secretion of pro-inflammatory cytokines, impaired cell-mediated immunity and neo-angiogenesis. Barnhart *et al.* (2002) found that compared with women with mild endometriosis, women with severe endometriosis have a statistically significantly lower pregnancy rate and implantation rate, have fewer oocytes obtained at ovarian retrieval, and have a lower peak estradiol concentration (Barnhart *et al.*, 2002).

Adhesion formation involves three important components: 1) acute inflammatory response, 2) fribinolysis, and 3) metalloproteinases and their tissue inhibitors. Celluler mediators within the peritoneal fluid can potentially modulate inflammatory responses over a large surface area due to the liquid nature of the peritoneal fluid. There are three important pro-inflammatory cytokines involved in adhesion formation: interleukine (IL)-1, IL-6 and Tumor Necrosis Factor (TNF)-α (Cheong *et al.*, 2002). Endometriosis is associated with signs of pelvic peritoneal inflammation including increased volume of peritoneal fluid, increased concentration of peritoneal fluid macrophages, and increased peritoneal fluid concentrations of IL-6, IL-8, TNF-α and other cytokines and growth factors. Indeed, these cytokines have been reported to increase the endometrial–peritoneal adhesion *in vitro* (D'Hooghe and Debrock, 2002). Pelvic adhesion secondary to endometriosis is the most accepted reason for infertility, presumably via dysfunction of the fallopian tube or ovary. Inflammatory cytokines, IL-6, IL- 8 and TNF-α produced by endometrial cells probably contribute to the adhesion process. IL-8 has been shown to stimulate the adhesion of endometrial cells to fibronectin. TNF-α has also been reported to promote endometrial stromal cell proliferation *in vitro* and endometrial stromal cell adhesion to extracellular matrix components (Garcia-Velasco and Arici, 1999). These pelvic adhesion inhibits ovum capture after ovulation.

Cysts of endometriosis (endometriomas) may become adherent to the uterus, bowel or pelvic side wall. Any of these anatomic distortions can result in infertility. The presence of an ovarian endometrioma greater than 1 cm in diameter is classified as stage III (moderate) or more in the revised American Society for Reproductive Medicine (ASRM) classification of endometriosis, but unfortunately, the staging system does not correlate well with a woman's chance of conception following therapy (ASRM, 2006). The impact of an ovarian endometrioma on infertility remains controversial, despite the number of studies that have been performed. Suzuki *et al* (2005) found that endometriosis, even after diagnostic laparoscopy with treatment when necessary, clearly affects the number of oocytes as well as the number of transferred embryos but not embryo quality and the related parameters of pregnancy, as indicated by the fertilization rate, embryo quality, implantation rate, pregnancy rate, and live birth rate, irrespective of the presence of an ovarian endometrioma (Suzuki *et al*, 2005). Nakahara (1998) found that the proportion of apoptotic bodies in the membrana granulosa cells and the cumulus cells from patients with endometrioma is significantly higher than that in patients without endometrioma. Based on these studies endometrioma prove the existence of a more advance stage of endometriosis than the non existence of endometrioma. The existence of endometrioma is considered one of the indicators of endometriosis in the ovary due to the increase of the apoptosis in the follicle and gave, in turn, the follicle an atretic status. Consequently, patients with endometriosis

with endometrioma had smaller numbers of follicles developed, oocytes harvested, and mature oocytes (Nakahara *et al*, 1998).

In women with endometriosis, pelvic adhesions contain estrogen and progesterone receptors, and produce basic fibroblastic growth factor and vascular endothelial growth factor, implying a regulation of pelvic adhesion formation by steroid hormone. Zang (2010) found that both the percentage and the density of protein gene product (PGP) 9.5-positive nerve fibres in ovarian endometriotic lesions were significantly higher in women with ovarian endometriosis who had pelvic adhesions than in those women with ovarian endometriosis and no pelvic adhesions (Zang et al., 2010). It is suggested that ovarian endometriotic lesions may be innervated through mediating effects of peritoneal inflammatory cytokines and growth factors including IL-1, IL-6 and TNF-a, in women with pelvic adhesions, thus leading to an increase of nerve fibres in ovarian endometriotic lesions in women with ovarian endometriosis (Zang *et al.*, 2010).

3. Abnormal folliculogenesis and impaired oocyte function

Infertility associated with the advanced stages of endometriosis may be explained by pelvic adhesion and endometrioma as described above. The mechanism of infertility associated with endometriosis without adhesion and endometrioma, such as minimal or mild endometriosis as well as the negative impact of all stages of the disease on infertility is poorly understood. Many possibilities have been suggested, ranging from abnormal folliculogenesis to impaired endometrium receptivity (Arici *et al.*, 1999). Peritoneal fluid, a biologic fluid present in the abdominal cavity, has been a focus of research on endometriosis because of the extent of information it potentially carries about the disease. The proximity of peritoneal fluid to endometriotic lesions shows the milieu in which the immune mediators associated with the local inflammation of endometriosis can be studied. It has been suggested that such alterations in cytokines and growth factors interfere with folliculogenesis, ovulation and fertilization (Arici *et al.*, 1999).

The local microenvironment of peritoneal fluid surrounding the endometriotic implant is immunologically dynamic and links the reproductive and immune systems. Peritoneal fluid contains a variety of free floating cells, including macrophages, mesothelial cells, lymphocytes, eosinophils and mast cells (Oral *et al.*, 1996). The peritoneal fluid of women with endometriosis have confirmed an increased number, concentration and activation of macrophages which may induce proliferation of cells that are involved in inflammation through secretion of factors such as IL- 1, IL-6, and TNF-α (Oral *et al.*, 1996a). Other studies similary found that levels of cytokines, such as, IL-6, IL-8 and TNF-α increased in the peritoneal fluid of women with endometriosis (Arici *et al.*, 1996), meanwhile endometriotic implants also secreted various cytokines including IL-1, IL-6, IL-8, TNF-α in the peritoneal cavity in patients with endometriosis (Oral *et al.*, 1996b). Cytokines, which are produced by many cell types in peritoneal fluid, play a diverse role as toxic effect in constructing the peritoneal environment that induces the development and progression of endometriosis and endometriosis-associated infertility (Harada *et al.*, 2001).

Peritoneal fluid bathed the ovaries, hypothetically the inflammatory components in peritoneal fluid in women with endometriosis might diffuse into the ovarian follicles, or by

paracrine mechanisms (Carlberg *et al.*, 2000) impair the granulosa cell function, oocyte maturation and folliculogenesis. Folliculogenesis is growth and development process of ovarian follicle consist of oocyte, granulosa and theca cells might result in mature and fertilizable oocyte (Rajkovic, 2006). The alteration of oocyte, granulosa, theca cells development and molecular follicular communication may impact on folliculogenesis. Carlberg (2000) found that granulosa cells of women with endometriosis have an up-regulated production of IL-1β, IL-6, IL-8, TNF-α which might be related to the reduced fertilization rate previously observed in endometriosis women (Carlberg *et al.*, 2000). Beside that women with endometriosis were reported having higher granulosa cell apoptosis rate and a lower percentage of G2/M phase granulosa cells compared with other group of infertile women. This result strongly suggest that the cytokines produced in endometriosis women may be responsible for the disturbance of the cell cycle in the granulosa cells as in other cells and in turn have pathogenic effects on folliculogenesis (Toya *et al.* 2000) . Nakahara (1998) found that higher incidence of apoptotic bodies correlates with a lower quality of oocytes in individual follicles. This study showed that the incidence of apoptotic bodies in membrana granulosa ovaries of patients with endometriosis undergoing the IVF-ET procedure was increased as the stage of the revised AFS classification advanced. It means that the quality of oocytes from patients with endometriosis decreases in proportion to advancing stages of the revised AFS classification and determine the degree of disturbance for folliculogenesis in the ovaries of the patients with endometriosis (Nakahara, 1998).

Our previous study postulated that apoptosis of granulosa cells caused disturbance in oocyte growth and maturation and associated with decreased growth differentiation factor-9 (GDF-9) production (Hendarto *et al.*, 2010). Oocyte-derived GDF-9 is obligatory for normal folliculogenesis and female fertility (Erickson and Shimasaki, 2001). Elvin (1999) reported that mouse GDF-9 can bind to receptors on granulosa cells, and plays multifunctional roles in oocyte-granulosa cell communication and regulation of follicular differentiation and function (Elvin *et al.*, 1999). In our study we found that the presence of GDF-9 in follicular fluid of preovulatory follicle was confirmed by western blotting analysis in a band of 53 kDa, and compared with the level in women with no endometriosis, GDF-9 level in the follicular fluid of women with severe endometriosis was lower. This might impair folliculogenesis, leading to reduced oocyte quality (Hendarto *et al.*, 2010). Our other study also comfirmed that oocyte-granulosa cell communication has already been altered showed by increasing the concentration of granulosa cell-derived kit-ligand in follicular fluid of infertile women with endometriosis (in publication process).

The cytoskeleton of metaphase II oocytes were influenced by rich pro-inflammatory factor present in peritoneal fluid of patients with endometriosis. By exposure of cryopreserved mouse oocytes to the peritoneal fluid from women with endometriosis, Mansour (2010) reported that in the endometriosis group, the cytoskeleton had a higher frequency of abnormal meiotic spindle and chromosomal misalignment, indicating severe damage compared with the control groups. The meiotic spindle plays a critical role in maintaining chromosomal organization and formation of the second polar body. Disorganization of the meiotic spindle can result in chromosomal dispersion, failure of normal fertilization, and

abnormal development. Alterations of the spindle may be one of the many causes related to infertility and/or recurrent pregnancy loss in patients with endometriosis (Mansour *et al.*, 2010). Reactive oxygen species (ROS) have been detected in peritoeal fluid of endometriosis patients but are not significantly elevated compared with the control and idiopathic infertility groups (Bedaiwy *et al.*, 2002). Reactive oxygen species have detrimental effects on oocytes, they are able to diffuse and pass through cell membrane and alter most types of cellular molecule such as lipids, proteins and nucleic acids. The consequences are mitochondrial alterations, embryo cell block, ATP depletion and apoptosis (Guerin, 2001).

Based on several studies above it is proposed that pro-inflammatory factors and ROS in follicular fluid women with endometriosis may diffuse and impact autocrine-paracrine communication of ovarian follicles causing cell-cycle alteration and an increased apoptosis in granulosa cells. Beside that, the presence of pro-inflammatory factors and ROS could influence the oocyte such as abnormal meiotic spindle, chromosomal misalignment and decreased GDF-9 production. Both may impair oocyte-granulosa cell communicatin and cause abnormal folliculogenesis and, in turn, result in reduced oocyte quality. Futher studies are needed. (see figure 1)

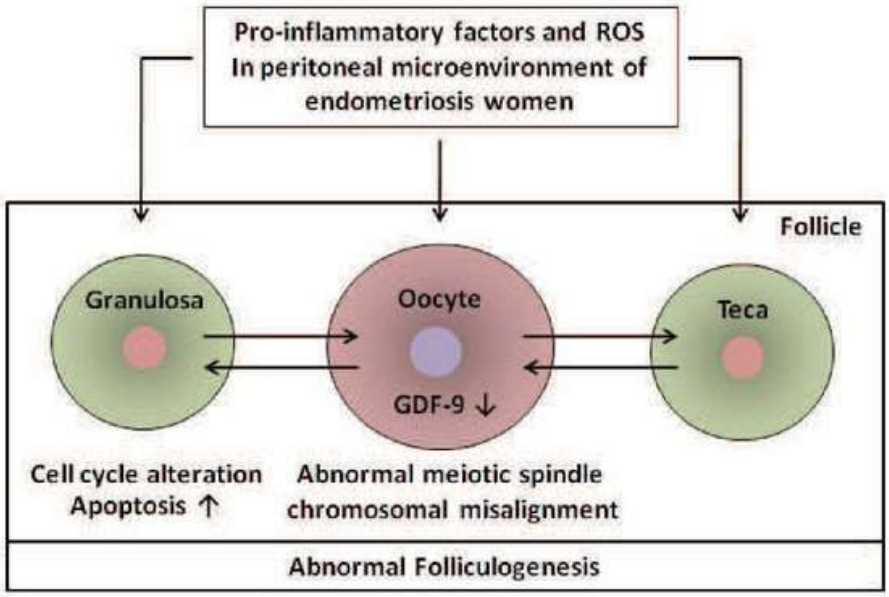

Fig. 1. Abnormal folliculogenesis in endometriosis (Hendarto, 2011)

4. Altered sperm function

Spermatozoa have to stay for a certain period of time in the female genital tract that normally favors capacitation, the ability to reach and fertilize the oocyte. The endometriosis-associated immuno-inflammatory changes in peritoneal fluid may have some adverse effects on spermatozoa (Carli *et al.*, 2007). Eisermann (1989) reported that levels of TNF-α of up to 800 U/ml in peritoneal fluid from infertile women with endometriosis higher than fertile women without endometriosis. In this concentration,

TNF-α caused a significant reduction in both progressive and total sperm motility when compared with controls group. Suggests that this may be a mechanism for the infertility observed in women with minimal endometriosis (Eisermann *et al.*, 1989). In the other study stated that the toxic effects of TNF-α could be the result of its ability to stimulate apoptosis in sperm cells through initiation of a caspase cascade. Exposing spermatozoa to pathological concentrations of TNF-α can result in significant loss of sperm function and genomic integrity. Infliximab, an TNF-α inhibitor, could potentially be used to help treat female infertility caused by endometriosis in those with elevated levels of TNF-α in their peritoneal fluid (Said *et al.*, 2005).

Another theory describing pathological effect of endometriosis on sperm function is the role of reactive oxygen species. Oxidative stress has been shown to exert toxic effects on sperm, damaging the sperm cell membrane, inducing DNA damage, and mediating sperm apoptosis (Agarwal *et al.*, 2006). Mansour (2009) found that progressive sperm DNA damage was significantly higher in samples incubated with peritoneal fluid from patients with endometriosis than those from healthy women. Spermatozoa are particularly susceptible to ROS-induced damage because their plasma membranes contain large quantities of polyunsaturated fatty acids and their cytoplasm contains low concentrations of the scavenging enzymes (Saleh *et al.*, 2002)

Reeve (2005) reported that significantly more spermatozoa bound per unit area to the ampullary epithelium of the uterine tubes taken from women with endometriosis, could potentially hinder fertilization by reducing the number of free spermatozoa in the tubal lumen that are available to take part in fertilization. Numerous studies have shown that spermatozoa that bind to the endosalpinx retain their viability, motility and fertilizing capacity longer than spermatozoa incubated alone or with other cell types. The aberrant expression of integrin in the endometrium of women with endometriosis would be speculated to increased sperm binding (Reeve *et al.*, 2005).

5. Reduced embryo quality

Use of IVF-ET as a therapeutic tool in endometriosis women with infertility could result in information about this disease and reproductive process aspects, such as folliculogenesis, fertilization, embryo development and implantation. The outcome of patients with endometriosis undergoing IVF-ET showed not only the influence of endometriosis on IVF result but also the possible pathomechanisms of infertility in endometriosis (Garrido et al., 2000). The impact of endometriosis in embryo development and quality is still on debate. Various embryo scoring system have been described to assess the developmental potential of embryos, but the most commonly used systems are the blastomeres cleavage rate, the shape and size of the blastomeres and the amount of anucleated fragment (Martynow et al., 2007)

Pellicer (1995) found a significantly reduced number of blastomeres in embryos from endometriosis patients compared with controls, and endometriosis patients had a poor IVF-ET outcome in terms of a reduced pregnancy rate per cycle, reduced pregnancy rate per transfer and reduced implantation rate per embryo replaced (Pellicer et al., 1995). Simon (1994) showed that patients who received embryos derived from endometriosis ovaries

showed a significantly reduced ability to implant compared with the remaining groups (Simon et al., 1994). These result above suggest that infertility in endometriosis patients may be related to alterations within the oocyte which, in turn, result in reduced embryos quality (Pellicer et al., 1995).

Endometriosis induces an inflammatory state by activation of macrophages, releasing ROS and cytokines (Gupta *et al.*, 2008). Macrophages, cytokines and other products present in the peritoneal fluid from patients with endometriosis could be responsible for a change in the peritoneal environment that generates embryotoxic activity. Torres (2002) found embryotoxicity was increased in women with endometriosis, but there was little correlation with severity of the disease. These study also found a significant increase in embryotoxicity in the presence of high cytokine concentrations, especially with IL-6 (Torres et al., 2002). Other study by Pellicer found progesterone concentrations in follicular fluid increased with the severity of endometriosis that may be related to the release of the cytokines. The result of the study also showed that IL-6 concentration was significantly increased in follicular fluid of patients with endometriosis, whereas VEGF accumulation in follicular fluid was significantly decreased in women with endometriosis compared with controls. The increased IL-6 means that the immune system may be activated as a marker of altered follicular function that result in reduced oocyte and embryo quality. The decreased VEGF concentration needs further investigation, but in IVF, elevated VEGF concentrations have been shown to be related to good follicular vascularization and health. The study by Pellicer concluded profound differences in the follicular environment of the oocytes of women with endometriosis, compared with those of healthy patients. It may be suspected as a marker of altered follicular function that result in reduced oocyte and embryo quality.

6. Impaired endometrium receptivity

There are controversial information regarding implantation alteration in endometriosis-associated infertility. Various studies described three causative factors: an oocyte/embryo impairment, endometrial defect and altered endometrial-embryonic cross-talk (Garrido *et al.*, 2002). Implantation depends on an interaction of the trophoblast with the uterine epithelium, whereas a receptive endometrium is characterized by abundant secretory activity such as the presence of several integrins including the αvβ3 integrin. Lessey (1994) reported that the majority of women with abnormal αvβ3 integrin expression had endometriosis stage I or II and stated that αvβ3 integrin expression could be a useful marker of mild endometriosis (Lessey *et al.*, 1994). Inconsistent result pointed by Surrey (2010) that a high prevalence of aberrant endometrial αvβ3 vitronectin expression was noted in a group of infertile endometriosis patients who are IVF candidates but there were no significant differences in ongoing pregnancy or implantation rates in those patients who failed to express integrin αvβ3 vitronectin who were treated with a 3-month course of a GnRH agonist before an IVF cycle in comparison to untreated controls. Endometrial αvβ3 integrin expression did not predict which patients would benefit from prolonged administration of a GnRH agonist before initiation of controlled ovarian hyperstimulation for IVF (Surrey *et al.*, 2010)

The detection of pinopodes as a possible marker of receptivity in humans has been extensively studied. Pinopodes are specialized cell surface formations presumably involved

in the adhesion of blastocysts to the luminal epithelium. Scanning electron microscopy in sequential endometrial biopsies showed that pinopodes formed briefly (1–2 days) and that their numbers correlate with implantation (Nikas *et al.*, 1999). Garcia-Velasco (2001) found pinopode expression in women with endometriosis did not differ from that of patients without endometriosis undergoing artificial cycles. Similarly, the clinical outcome in these women was comparable to that of the general population included in the oocyte donation program and this study stated that pinopode expression is not altered, suggesting that endometrial receptivity in women with this disease remains unaltered (Garcia-Velasco *et al.*, 2001).

Endometrial aspects and molecular studies on the receptivity status of endometrium resulted in conflicting data. Several studies suggest that an altered follicular microenvironment could be responsible for a defective folliculogenesis, and subsequently reduced oocyte/embryo quality, and in turn, result in altered embryo implantation but the debate still ongoing (Garrido *et al.*, 2002).

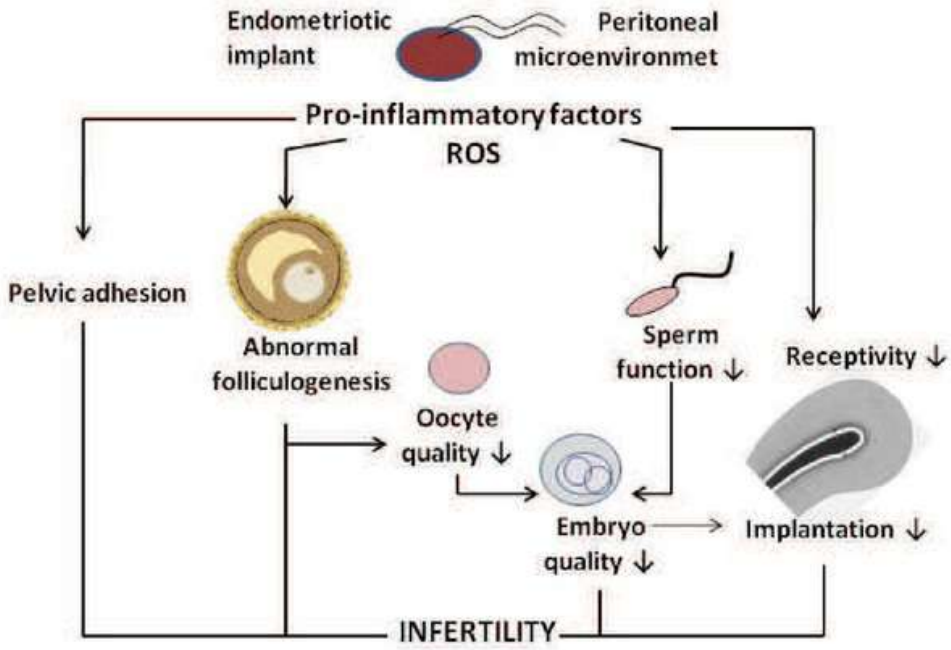

Fig. 2. Pathomechanism of infertility in endometriosis (Hendarto, 2011)

7. Summary

We have reviewed various studies with regard to the understanding of pathomechanism of infertility in endometriosis, based on its impacts on number of pathologic conditions, such as: pelvic adhesion and endometrioma, abnormal folliculogenesis and impaired oocyte function, altered sperm function, reduced embryo quality, and impaired endometrium receptivity. The controversy regarding whether endometriosis is a cause of infertility or an incidental finding is ongoing.

Based on several studies reviewed above showed that peritoneal microenvironment of women with endometriosis which contain pro-inflammatory factor and ROS is the main causative factor of the pathomechanism of infertility in endometriosis. They have a key role through autocrine-paracrine communication alteration in the mechanism of pelvic adhesion, abnormal folliculogenesis, reduced oocyte/embryo quality, reduced sperm fuction and implantaion impairment (see figure 2). We hope that the increase of our understanding on the above pathomechanism can increase our attention to the improvement of the complex management of infertility in endometriosis.

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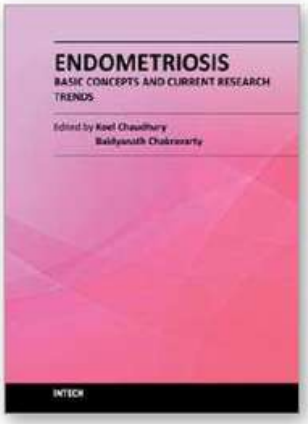

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Edited by Prof. Koel Chaudhury

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This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal aspects related to the disease pathogenesis; recent research reports on infertility, endometrial receptivity, ovarian cancer and altered gene expression associated with endometriosis; various predictive markers, and imaging modalities including MRI and ultrasound for efficient diagnosis; as well as current non-hormonal and hormonal treatment strategies This book is expected to be a valuable resource for clinicians, scientists and students who would like to have an improved understanding of endometriosis and also appreciate recent research trends associated with this disease.

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