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# Alteration in Endometrial Remodeling: A Cause for Implantation Failure in Endometriosis?

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## 1. Introduction

### 1.1 Implantation failure in endometriosis

The process of implantation is an interactive cascade of events between the embryo and the endometrium. It is a dynamic process consisting of three distinct phases. They are (i) apposition of embryo (ii) attachment with the epithelial lining of the endometrium and (iii) invasion into the endometrial stroma gaining access to the maternal circulatory system. Embryo implantation failure may occur due to embryonic defect or unsupportive endometrium. Advances in Assisted Reproductive Technology (ART) have made it possible to obtain good quality embryos; however, successful implantation remains the bottleneck for a successful pregnancy. The endometrium remodels before attaining a state of receptivity. Endometrium remains receptive during a limited period, when it is favourable for blastocyst attachment and implantation. In women, there is clinical evidence of a brief period of optimal uterine receptivity which allows for blastocyst implantation. This period, called the implantation window, is related to changes in the endometrial epithelial morphology. Inappropriate morphological development leads to unreceptive endometrium that causes defective endometrial /embryonic cross talk. This is generally agreed to be one of the main reasons for implantation failure. Endometriosis, characterized by benign growth of endometrial tissue outside the uterus, affects approximately 20%–48% of women during their reproductive years. The occurrence of aberrant hormonal, immunological, genetic and pathophysiological events associated with endometriosis is attributed to the heterogeneous etiology of the disease. The symptoms of endometriosis do not depend on the severity or stage of the disease. Women with even mildest degree of endometriosis can have a 3 – 4 fold reduction in their annual birth rate compared to normal non-endometriotic women.

Presence of endometriosis alters the characteristic of the endometrium. It also affects the expression of various factors and markers of receptivity during implantation window. All these result in dysfunctional endometrium. This can be a cause of higher implantation failure rates and lower pregnancy rates in endometriotic women due to failure of embryo implantation. However, alterations in endometrial remodeling in endometriosis resulting in impairment of the endometrial receptivity is still poorly understood. An understanding of endometrial receptivity in women with endometriosis is, therefore, crucial in understanding the fundamental causes of implantation failure which in turn, may have significant implications on fertility potential of these women.

## 2. Matrix turnover and angiogenesis during implantation

### 2.1 Matrix turnover in endometrium and implantation

The unique characteristic of the endometrial tissue is that it undergoes cyclic degeneration and regeneration in each menstrual cycle. The endometrium consists of a layer of columnar epithelium bedded on a layer of connective tissue. The extracellular matrix (ECM), which forms a component of the connective tissue, provides the scaffolding for the anchorage of the cells within the tissue (McIntush and Smith 1998) and presents a locale for cellular migration, division and differentiation (Birkedal-Hansen et al., 1993). The extensive remodeling of the connective tissue of the endometrium requires both the degradation and reformation of the ECM which is accomplished by highly regulated turnover of the ECM (Hulboy et al., 1997). This destruction of the ECM occurs by the action of a class of proteolytic enzyme identified as matrix metalloproteinases (MMP). MMPs and the tissue inhibitors of metalloproteinases (TIMP) regulate a number of aspects of reproductive physiology like dynamic remodeling of the ovary and endometrium throughout each menstrual cycle, implantation, embryonic development and parturition. There exists equilibrium between the MMPs and TIMPs action for controlling this turnover of the ECM. Any circumstances that may bring about interruption of this delicate balance leads to a number of pathological complexities related to pregnancy and infertility like luteinized unruptured follicle syndrome, ovarian cysts, endometriosis, uterine fibroids, inappropriate implantation resulting in tubal pregnancy or spontaneous abortion, premature rupture of fetal membranes, or carcinoma of the ovary or uterus (Curry and Osteen 2003).

Several studies have reported the diverse pattern of MMPs expression in the endometrium throughout the menstrual cycle. Since breakdown of the endometrial lining occurs during menstruation, several MMPs are reported to be highly expressed during this phase. However, their expression gradually falls off during rest of the cycle. Nevertheless various MMPs are observed to express at various phases of the cycling endometrium. Expression of MMP-2 remains consistent throughout the whole cycle along with TIMP-1 and TIMP-2. Endometrial MMP-9 expression shows a cyclical change in its distribution between glandular and stromal cells. It expresses in the endometrium throughout the cycle, however, its expression increases during midsecretory phase particularly in the glandular cells (Hulboy et al., 1997). Although the association of MMP-2 and -9 and their endogenous inhibitors in pathogenesis of infertile condition like endometriosis is well established (Salata et al., 2008), knowledge regarding their involvement in endometrial remodelling during implantation window in endometriotic women is limited.

### 2.2 Angiogenesis

Endometrial remodeling involves proliferation of its functional layer upon estrogen enhancement (Groothuis et al., 2007) and differentiation by the influence of progesterone from the luteinized follicles (Okada et al., 1999). This is followed by the degeneration of this superficial layer and again reconstruction of the new one. These constant cyclic changes of the endometrium are associated with angiogenesis and neovascularisation (Perrot-Applanat et al., 2000). Vascular endothelial growth factor (VEGF) is a prime angiogenic stimulus for vascular permeability based on its capability to bring on vascular leakage (Ferrara and Davis-Smyth 1997, Ferrara et al., 2003). VEGF regulated angiogenesis and neovasculogenesis of the endometrial tissue is elemental for the growth and differentiation of the endometrium for implantation and placentation (Giudice 1996, Perrot-Applanat 2000). Due to its control

over the human reproductive cycle, VEGF is present in the stromal and glandular epithelium of the human endometrium throughout all phases of the menstrual cycle (Torry and Torry 1997, Smith 1998, Shifren et al., 1996, Charnock-Jones 1993, Popovici 1999, Lockwood 2002). However there exists a strong debate regarding its expression and angiogenesis. VEGF expression increased in the late secretory phase and heightened during menses (Torry and Torry 1997, Charnock-Jones 1993, Popovici 1999, Lockwood 2002, Bausero 1998). There is a marked increase even in the vascular network of the endometrium during the secretory phase over the proliferative phase (Ota 1998). But Nayak and Brenner reported that during proliferative phase there is a noted increase in the VEGF expression in stroma which shifts to glandular epithelium during the secretory phase (Nayak and Brenner 2002). However, contradictory report exist indicating that a gradual decline in angiogenesis occurs at the end of the cycle which rapidly increases with the start of a new cycle and reaching a maximum height during the mid cycle (Au and Rogers 1993). Other investigators have suggested that VEGF expression remains inconsistent (Sugino et al., 2002) or there is no change in the vascularity throughout the endometrial cycle (Rogers and Au 1993).

## 2.3 Regulation of matrix remodeling

It is suggested that inappropriate regulation of sex steroids may lead to defect in implantation. The role of estradiol in embryo implantation is a subject of controversy and its association with pregnancy outcome in IVF cycle is an area of research for many years (Kyrou et al 2009). Several studies have shown that midluteal decline of serum estradiol do not affect the endometrial development, embryo implantation and IVF outcome (Friedler et al., 2005; Narvekar et al., 2010; Hung et al., 2000). This may be due to the fact that during follicular phase, estradiol induces growth of follicles, preparation of endometrium and production of specific proteins, growth factors and receptors of estrogen and progesterone. Additionally, adverse effect of high estradiol level on endometrial receptivity is still under debate (Kyrou et al., 2009). A number of investigators found no effect of high estradiol levels on the treatment outcome of IVF/ICSI cycle (Sharara and McClamrock 1999, Kosmas et al., 2004). Some studies have, however, suggested that elevated levels of estradiol may be responsible for impaired endometrial receptivity (Simon et al., 1995; Valbuena et al., 2001; Kyrou et al., 2009). After ovulation, progesterone is the main contributory sex hormone executing the transformation of the endometrium during the secretory phase.

It is evidenced that expression of cyclooxygenase-2 (COX-2), a molecule associated with angiogenesis and cell differentiation, promotes the release of MMP-2 (Xiong et al., 2005) and -9 (Itatsu et al., 2009), and angiogenic factor VEGF (Wang *et al.* (2010). COX-2, on the other hand, is regulated by female sexual hormone estradiol and progesterone (Li et al., 2007). Since the process of angiogenesis during endometrial remodelling shares similarities with the process of angiogenesis during metastasis in cancer, estradiol may also be involved in the up-regulation of the gene expression of COX-2 and MMPs during embryo implantation. Involvement of COX-2 gene in embryo implantation is a subject of interest among the researchers working on endometrial receptivity, and is suggested to play an important regulatory role in successful implantation. However, little is known about its role in endometrial receptivity in women with endometriosis.

## 2.4 Endometrial receptivity markers

Inadequate uterine receptivity and poor embryo formation are two major factors responsible for implantation failure (Simon et al., 1998; Ledee-Bataille et al., 2002). Nowadays, using

ART procedure, clinicians can improve embryo formation considerably; however, no therapies are available to make the endometrium more receptive. Expression of various implantation markers and proteins lead to remodeling of the endometrial matrix thereby transforming the endometrium towards a receptive milieu. Several molecular repertoires expressed during the implantation window are considered to be useful markers of implantation. Expression of various markers including pinopodes $\alpha_v\beta_3$ integrin, LIF, L-selectin ligand and Mucin-1 throughout the different stages of implantation are considered to be responsible for endometrial receptivity.

### 2.4.1 Pinopodes

Pinopodes, also known as uterodomes, are large cytoplasmic protrusions from the endometrial epithelial surface and are several micrometers wide. These are specialized cell structures that are involved in adhesion and penetration of the blastocyst into the stroma. These structures project into the uterine lumen and are above the microvilli level. Their expression is limited to a maximum period of 2 days during the menstrual cycle corresponding to the presumed window of implantation (Stavreus-Evers et al., 2001). Endometrial pinopodes development is associated with the mid-luteal phase increased expression of leukaemia inhibitory factor (LIF) and its receptor (Aghajanova et al., 2003), progesterone (Stavreus-Evers et al., 2001) and integrin $\alpha_v\beta_3$ (Lessey et al., 1992). Advocated as a marker of uterine receptivity, their expression, has been investigated solely by means of scanning electron microscopy (SEM) (Develioglu et al., 2000).

### 2.4.2 Integrins

Integrins are surface ligands, usually glycoproteins, belonging to the class of cell adhesion molecules (CAM). An integrin molecule consists of two different, non-covalently linked $\alpha$ and $\beta$ subunits that are paired to form various heterodimers with distinct function (Hynes, 2002). At least 20 types of integrin heterodimer have been defined, which form from 14$\alpha$ and 9$\beta$ subunits (Lindhard 2002). Integrins are unusual cell surface receptors in that they bind with low affinity and are present in large numbers, allowing for ligand motility without loss of attachment. Endometrial epithelial cells constitutively express certain integrins, whereas others are cycle dependent (Lessey 1992). $\alpha_v\beta_3$, an example of the latter is present on the apical surface of both luminal endometrial cells and human embryos. 41 different aberrant expressions of this integrin are reported in women with endometriosis (Lessey et al., 1994).

### 2.4.3 LIF

LIF is a member of the IL-6 family and is secreted by the endometrial epithelium, CD16–CD56 natural killer cells and type 2 T-helper cells. Animal and human studies indicate that LIF plays an important role in implantation and for pregnancy to occur (Lass et al., 2001). LIF protein can be detected by immunohistochemistry in the luminal, glandular and stromal epithelium. There is very little LIF expression in proliferative endometrium, but levels increase during the secretory phase, reaching a maximum between days 19 and 25, which coincides with the implantation window (Charnock-Jones 1994).

### 2.4.4 Mucins

Mucins are high molecular weight (MW) glycoproteins, which contain at least 50% of carbohydrate O-linked to a threonine/serine rich peptide core (Gendler et al., 1990). Among

the 14 cloned human mucins, only Mucin-1 (MUC1) and to a lesser extent MUC6 have been found in the human endometrium (Gipson et al., 1997). Cell–cell and cell–matrix adhesion are inhibited in direct correlation to the length of the MUC-1 ectodomain (Hilkens et al., 1992; Wesseling et al., 1996).

### 2.4.5 L-Selectin ligand

Selectins are glycoproteins which also belong to the CAM family. The expression of selectin oligosaccharide-based ligands, such as MECA-79 or HECA-452, is up-regulated during the window of implantation (Genbacev et al., 2003). MECA-79 is immunolocalized in the luminal and glandular endometrial epithelium throughout the menstrual cycle, although the staining considerably intensifies during the mid-secretory phase. The physiological importance of the interaction between L-selectin and its oligosaccharide ligands has been investigated in the human endometrium (Genbacev et al., 2003).

Though several studies investigating endometrial receptivity during implantation window are documented, the mechanism responsible for implantation failure in endometriosis is still poorly understood. Expression of various cell adhesion molecules and pinopodes in women with endometriosis is explored in the present study. Since, COX-2 is reported to be physiologically involved in the process of angiogenesis (Matsumoto et al., 2002), and in view of the fact that angiogenesis is essential for endometrial remodeling, we were motivated to assess the expression of various angiogenic factors including VEGFR, MMP-2,-9 and their tissue inhibitors in women with endometriosis during the implantation window. Additionally, expression of COX-2 was studied to assess their associated regulatory role in the process of endometrial remodeling during implantation window.

## 2.5 Material and method

### 2.5.1 Subject selection

30 women with endometriosis and 20 without the disease were included in the study. Presence/absence of endometriosis was confirmed by diagnostic laparoscopy. It was ensured that these women had not received any kind of medical or hormonal treatment during the past three months. Women with history of chocolate cyst removal, previous history of any surgery, with other possible causes of pain or pelvic pathology including pelvic tuberculosis were excluded.

### 2.5.2 Sample collection

Blood samples collected from patients were allowed to clot and the serum separated by centrifugation at 3,000 rpm for 5 min at 4°C. Serum samples were stored at -20°C until further use. Endometrial biopsy was performed on the 7th day after confirmation of ovulation. The collected tissue was washed in phosphate buffer saline (PBS) and divided into three parts: one part was used for stromal and epithelial cells isolation for flow cytometric analysis of different molecular repertoires of the endometrium, the other part was fixed for immunohistochemistry (IHC) and scanning electron microscopy of these receptivity markers. From the third part, RNA was isolated immediately.

### 2.5.3 Isolation of cells and flow cytometric analysis

Endometrial tissue was first digested in 2% collagenase-1 (Invitrogen, Grand Island, NY, USA) in DMEM (Himedia, Mumbai, India) for 1.5 to 2 hrs at 37°C and then centrifuged to isolate the stromal cells. Undigested glands were then treated with 0.25% trypsin-0.02% EDTA (Himedia, Mumbai, India) for 4–8min, washed with 10% FBS-DMEM. Single epithelial cells were isolated by centrifugation, as described previously. Isolated cells were washed, RBC lysed using RBC lysis solution and fixed in 2% paraformaldehyde (20 min at RT). Single cell suspension thus obtained was divided into five parts; four parts were stained with mouse anti-human $\alpha_v\beta_3$ integrin, LIF (R&D Systems, Minneapolis, MN, USA), Muc-1 (Abcam, Cambridge, UK) and rat anti-human MECA-79 monoclonal antibody (Santa Cruz 1 Biotechnology, Inc., Santa Cruz, California, USA) according to instructions provided by the manufacturer in the manual. The fifth part remained unstained. Excess antibodies were washed out and the cells again incubated with fluorescein conjugated secondary goat anti-mouse and anti-rat IgG (R&D Systems, Minneapolis, MN, USA). After washing excess antibodies, the stained cells were analyzed using flow cytometer (BD FACS Calibur™, BD Biosciences, San Jose, CA, USA).

### 2.5.4 Immunohistochemistry

3-5 μm thick sections obtained from formaldehyde fixed, paraffin-embedded tissue were dehydrated in graded ethanol. After antigen retrieval, slides were blocked using 3% BSA in PBS and incubated with mouse anti-human $\alpha v\beta 3$ integrin (R&D Systems, Minneapolis, MN, USA), Muc-1 (Abcam, Cambridge, UK), LIF and rat anti-human MECA-79 monoclonal antibody (Santa Cruz biotechnology, INC., Santa Cruz, California, USA). Excess primary antibody was washed with PBS and the sections were again incubated with anti-mouse and anti-rat biotinylated secondary antibody (Santa Cruz biotechnology, INC., Santa Cruz, California, USA) according to the manufacturer's protocol, before incubation with avidin biotinylated horseradish peroxidase (Santa Cruz biotechnology, INC., Santa Cruz, California, USA). Labeled cells were visualized with Diaminobenzidine (DAB) and sections counterstained with hematoxylin. Next, the slides were dehydrated using series of alcohol gradient and mounted using distrene, tricresyl phosphate (DPX) and xylene. The slides were then examined under bright field microscope (Carl Zeiss, Jena, Germany).

### 2.5.5 Scanning electron microscopy

Formaldehyde-fixed tissues were washed in PBS and dehydrated in a series of alcohol gradient (50%, 70%, 90%, 95%, 100%), each for 10 mins, dipped in HMDS (1,1,1,3,3,3-hexamethyl disilazane; SRL, Bombay, India) and air dried. Dried tissues were then mounted and coated with gold and the luminal endometrial surface thoroughly examined under SEM (Jeol JSM-5800 Scanning Microscope, Tokyo, Japan). Pinopode formation was also evaluated semi-quantitatively depending on their stage of development on the surface of the endometrium, and scored as (i) well-developed (ii) poorly developed and (iii) absent and on their abundance and scored as (i) abundant (ii) moderate (iii) few.

### 2.5.6 Real-time PCR

Levels of COX-2, MMP-2, -9, TIMP-1 and -2 gene expression were analyzed by real time PCR (RT-PCR), which was performed with ABI Prism 7000 Sequence Detection System (Applied Biosystems Inc., Carlsbad, California, USA) using syber green master mix (Applied Biosystems Inc., Carlsbad, California, USA). RT-PCR primers were designed using

sequence data. Total RNA was isolated from tissue by RNA isolation kit (Trizol Reagent, Invitrogen, Carlsbad, California, USA) and 10 μl of total RNA isolated was subjected to reverse transcription for cDNA synthesis with High-Capacity cDNA Reverse Transcription Kits (Applied Biosystems, Carlsbad, California, USA), according to the manufacturer's instructions. After synthesis, 5 μl of cDNA was used for the RT-PCR mixed with syber green. At the end of each reaction, Cycle threshold (Ct) was manually set at the level that reflected the best kinetic PCR parameters, and melting curves were acquired and analyzed. Relative quantification was used to measure gene expression by relating the PCR signal.

### 2.5.7 Western blotting

The endometrial tissue was homogenized in tissue lysis buffer. The tissue lysate was then centrifuged at 15,000 g for 15 min and the protein concentration of the homogenates was determined by the GeNei™ Protein Estimation Kits (Bangalore Genei, India). 30 μg of homogenate protein were separated by SDS-polyacrylamide gel electrophoresis (SDS- PAGE). The separated proteins were electroblotted onto a Hybond PVDF membrane (GE Healthcare) at 30 volt for 13 hrs. After blocking the non-specific binding sites with non-fat dry milk in TBST buffer for 1 hr at room temperature, the blots were incubated overnight at 4°C with rabbit polyclonal antibody against COX-2, mouse monoclonal antibody against MMP-2,-9, TIMP-1 and -2 (Santa Cruz Biotechnology Inc, Santa Cruz, CA, USA), rabbit polyclonal antibody against VEGF, VEGFR1+VEGFR2 (Abcam, Cambridge, UK). The blots were then washed three times with TBST buffer, incubated for 1 hr at room temperature with horseradish peroxidase-linked goat anti-rabbit immunoglobulin G (IgG) and goat anti-mouse immunoglobulin G (IgG) (Santa Cruz Biotechnology Inc, Santa Cruz, CA, USA). After further washing, the immunoreactive proteins were revealed using the DAB as substrate.

### 2.5.8 Statistical analysis

Data were compared using independent two sample't' test and chi-square test, as applicable. Ky Plot version 2.0 beta 13 software and Graphpad Prism Software were used for this purpose. Statistical significance was defined as $p \leq 0.05$.

## 3. Result

The clinical characteristics such as age, BMI, endometrial thickness, serum estrogen and progesterone levels of women participating in this study are summarized in Table I.

| Parameters | Endometriosis | Control | P value |
|---|---|---|---|
| Age | 29.5±0.61 | 29.32±0.83 | P>0.05 |
| BMI | 28.18 ± 0.7 | 26.51 ± 0.6 | P>0.05 |
| Endometrial thickness (cm) | 9.25 ± 0.25 | 8.25 ± 0.41 | P>0.05 |
| Serum estrogen level (pg/ml) | 258.5 ± 13.83 | 193.6 ± 14.66 | P≤0.05 |
| Serum progesterone level (ng/ml) | 12.39 ± 1.28 | 26.43 ± 2 | P≤0.05 |

(Mean ± SEM)

Table 1.

Low levels of immunoreactivity of the endometrial receptivity markers including $\alpha_v\beta_3$ integrin, LIF, L-selectin ligands (MECA-79) and Muc-1 were observed in women with

endometriosis in contrast to strong immunoreactivity of controls. In addition, mean expression of these molecular markers detected by flow cytometric analysis shows a significantly lower expression both by the stromal and epithelial cells in women with endometriosis as compared to controls.
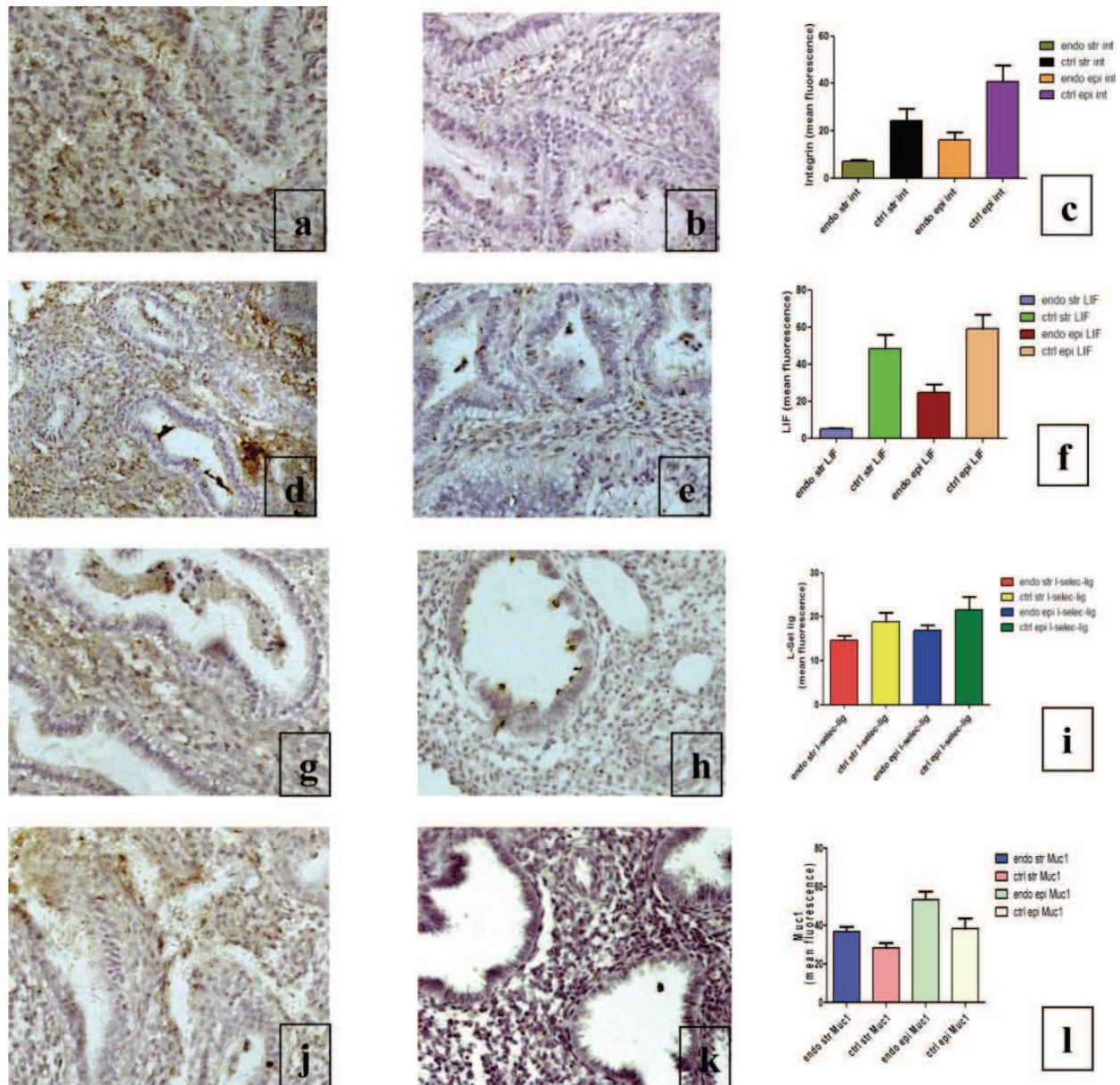


Fig. 1. Immunohistological images of different biochemical markers expression.
**a**. $\alpha_v\beta_3$ integrins in control  **b**. $\alpha_v\beta_3$ integrins in women with endometriosis **c**. Graphical representation of $\alpha_v\beta_3$ integrin expression in  the stromal and epithelial cells of endometrial tissues in endometriosis and control **d.** LIF in control **e.** LIF in women with endometriosis **f.** Graphical representation of LIF expression in  the stromal and epithelial cells of endometrial tissues in endometriosis and control **g**. L-selectin ligand in control  **h**. L-selectin ligand in women with endometriosis **i**. Graphical representation of L-selectin ligand expression in  the stromal and epithelial cells of endometrial tissues in endometriosis and control  **j**. Muc1 in control  **k**. Muc1 in women with endometriosis **l**. Graphical representation of Muc1 expression in  the stromal and epithelial cells of endometrial tissues in endometriosis and control.

Further, few poorly developed pinopodes were seen in women with endometriosis as compared to controls, which showed abundant well formed pinopodes (Figure 2, 3 and 4).
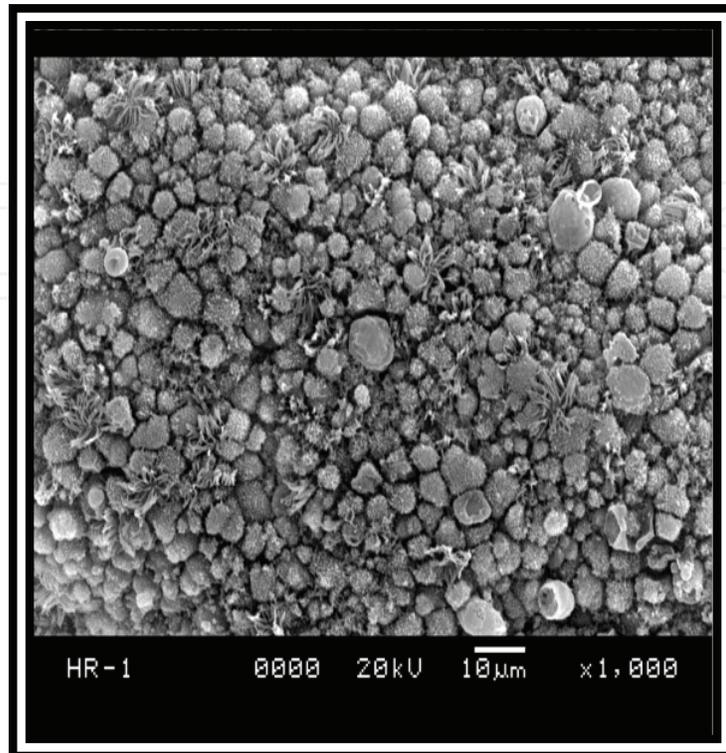


Fig. 2. Well developed pinopodes in control
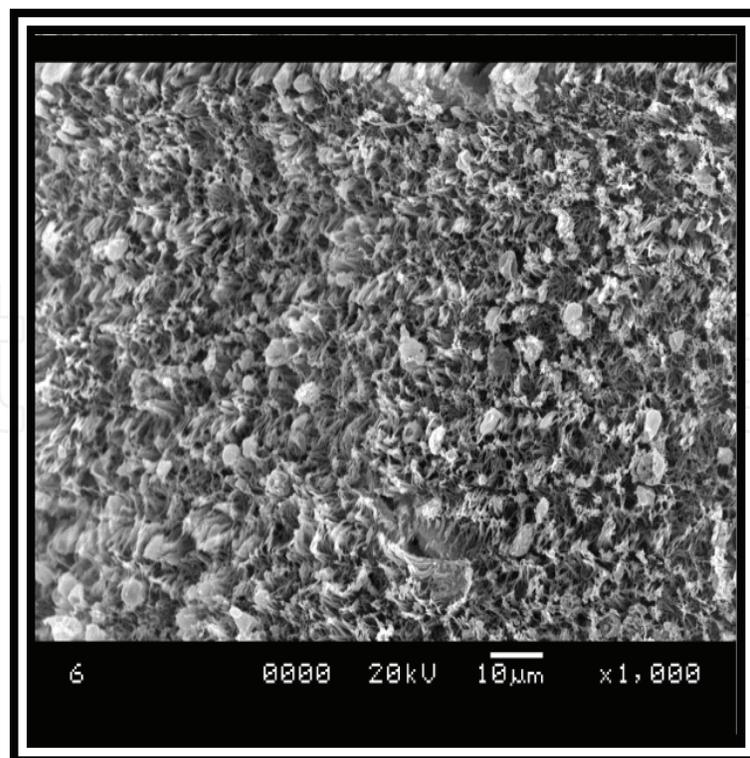


Fig. 3. Poorly developed pinopodes in endometriosis
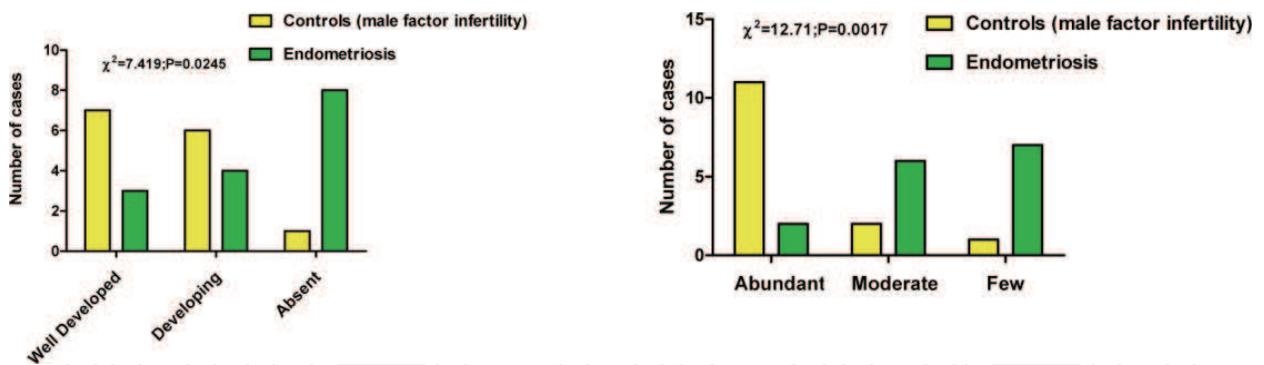
Fig. 4. Graphical representation of pinopode expression in the endometrial tissues in endometriosis and controls.

A significant increase in endometrial MMP-2, -9 and decrease in TIMP-1 and -2 expressions, were observed in women with endometriosis when compared to controls. Further, the endometrial expression of COX-2 was observed to be higher in women with endometriosis when compared with controls.
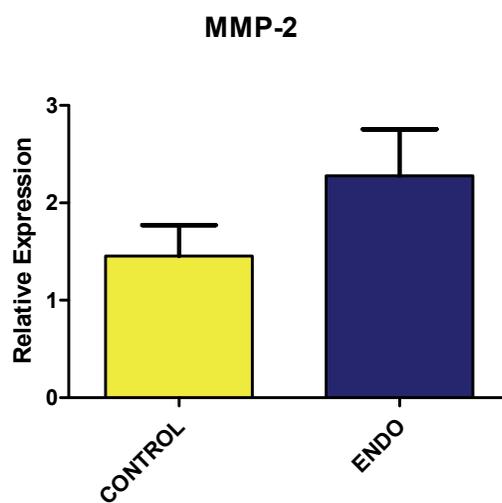


Fig. 5. Expression of MMP-2 gene in endometriosis and control
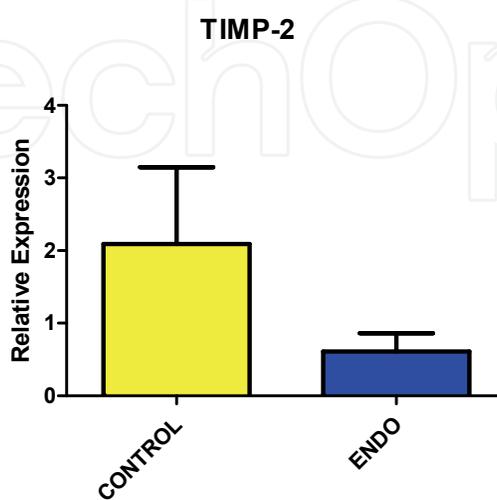


Fig. 6. Expression of TIMP-2 gene in endometriosis and control
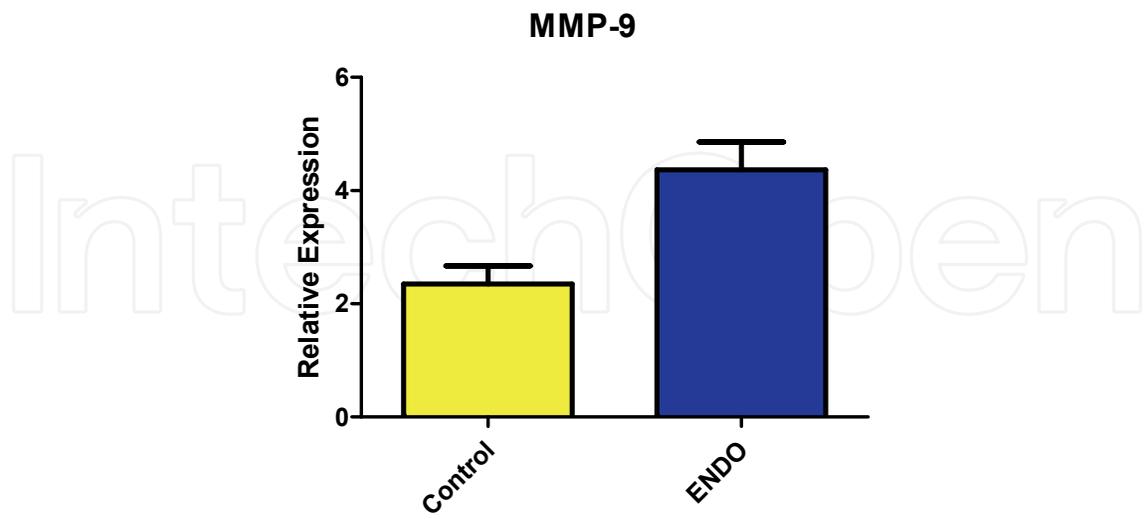
Fig. 7. Expression of MMP-9 gene in endometriosis and control
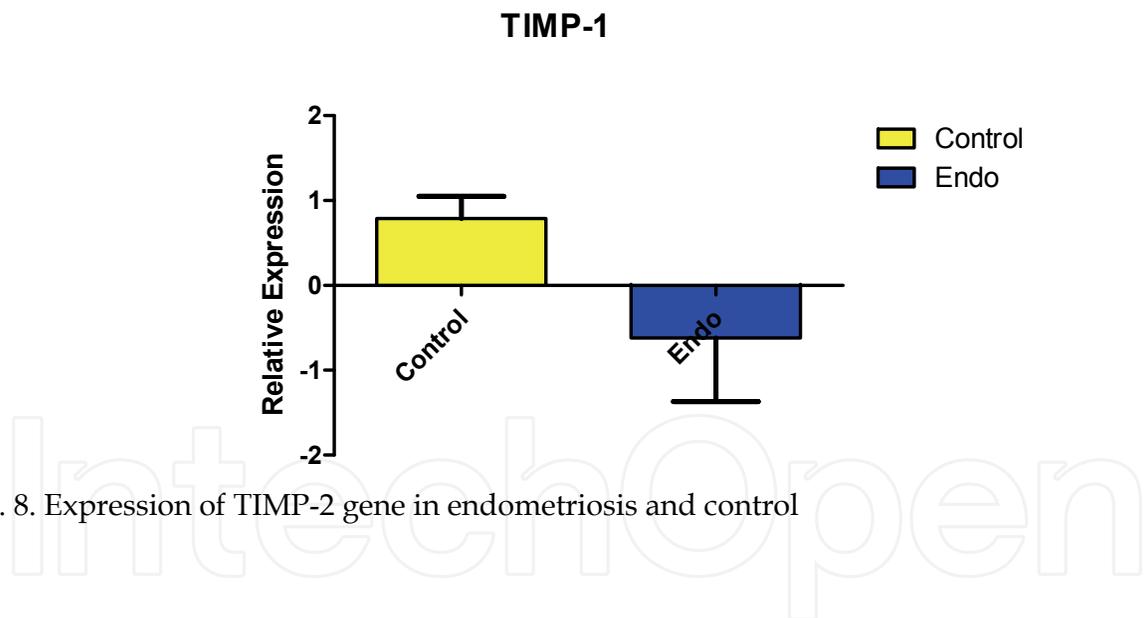


Fig. 8. Expression of TIMP-2 gene in endometriosis and control



Fig. 9. Expression of MMP-2 and -9 in endometriosis and control

Fig. 10. Expression of TIMP-1 and -2 in endometriosis and control
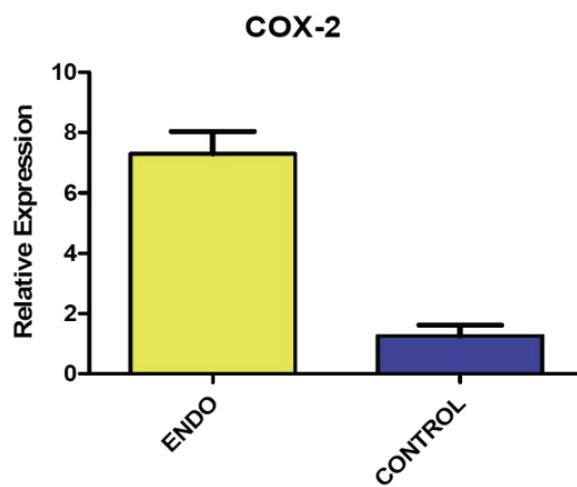


Fig. 11. Expression of COX-2 gene in endometriosis and control
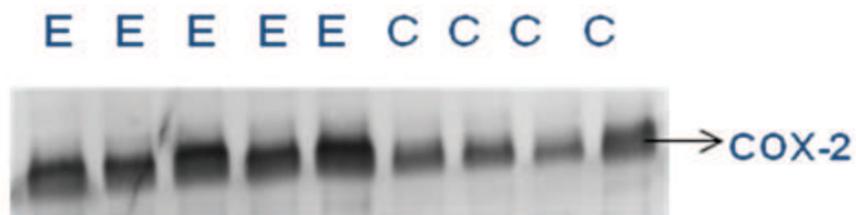


Fig. 12. Expression of COX-2 in endometriosis and control
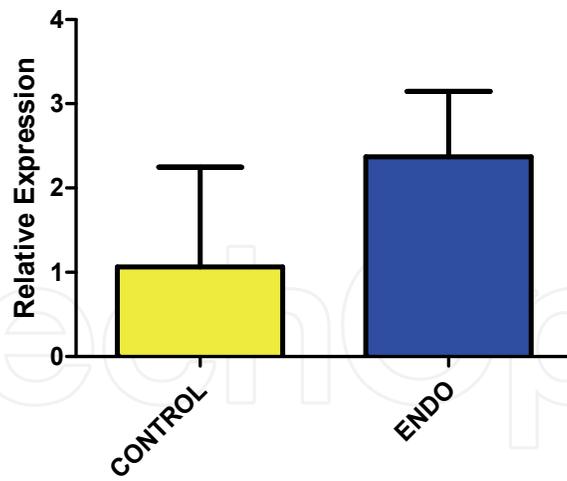
Fig. 13. Expression of VEGFR-1 gene in endometriosis and controls
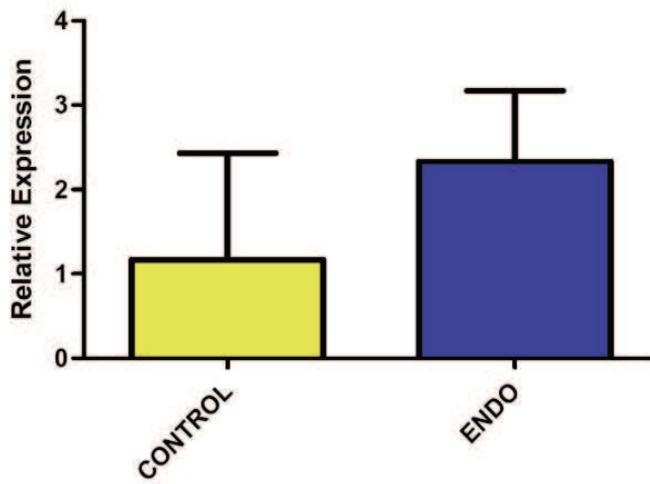


Fig. 14. Expression of VEGFR-2 gene in endometriosis and controls
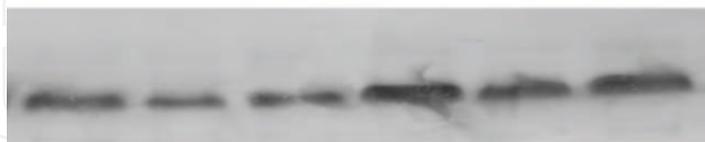


Fig. 15. Expression of endometrial VEGF in endometriotic women and control



Fig. 16. Expression of endometrial VEGFR in endometriotic women and control

Endometrial expression of VEGF and its receptors VEGFR1 and VEGFR2 were observed to be lower and higher respectively in women with endometriosis when compared with controls.

## 4. Proposed molecular mechanism for implantation failure in endometriosis and future treatment strategies

In the present study, a hypothesis correlating various factors responsible for implantation failure in endometriosis is proposed (Figure 16). It is well established that endometriosis is an estrogen-dependent disorder. As mentioned earlier, estrogen regulates the expression of MMP-2 and MMP-9 in matrix turnover and VEGF mediated angiogenic activities in various physiological and pathological conditions. Based on our findings, we hypothesize that dysregulation of sex steroids induces over-expression of COX-2 in the endometrium of women with endometriosis. This, in turn, affects endometrial remodelling by up-regulating the expression of MMP-2 and -9, the major molecules responsible for matrix degradation and also increases the expression of VEGF and its receptors, considered to be key angiogenic molecules. This hypothesis is further evidenced by abnormal expression of implantation markers in these women suggesting poor endometrial receptivity and high rate of implantation failure. Molecules which can effectively control excessive endometrial matrix degradation by inhibiting over-expression of various factors responsible for matrix turnover and angiogenesis may be considered as a new therapeutic option for the treatment of endometriosis.
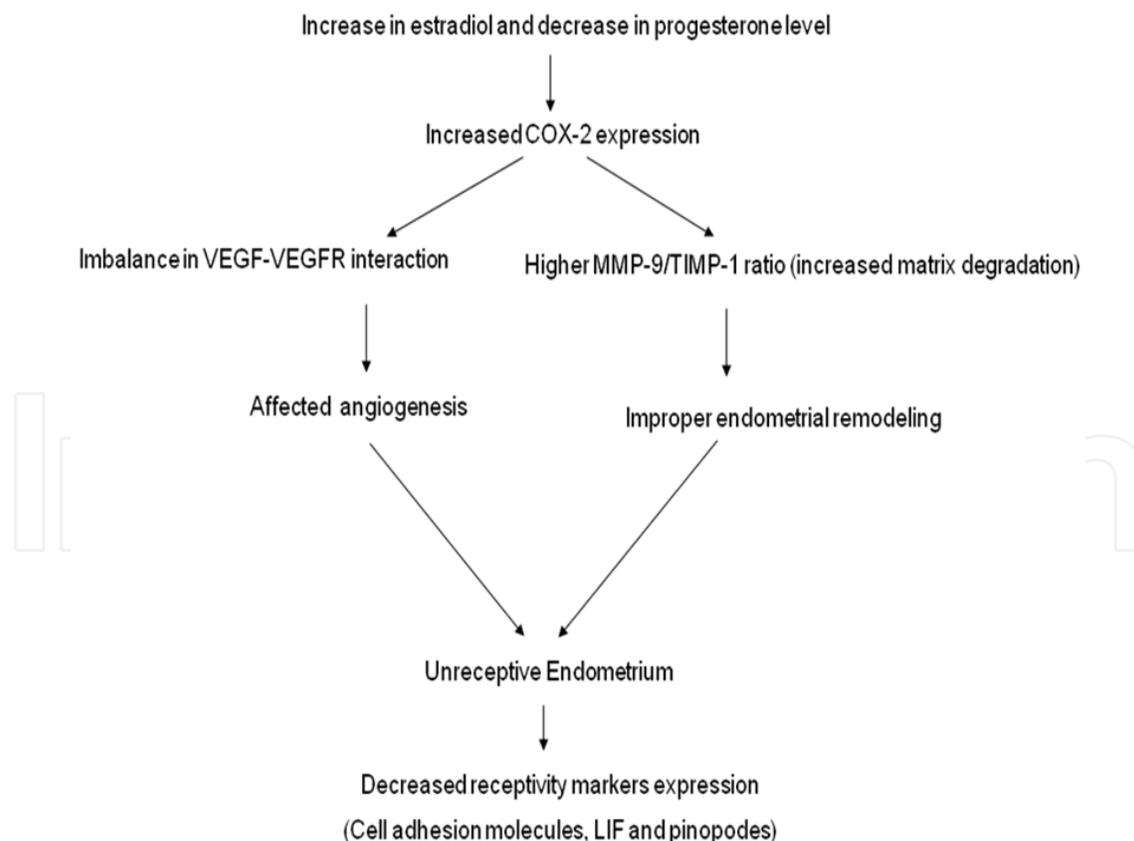


Fig. 16. Schematic representation of the molecular mechanism regulating the process of endometrial receptivity in endometriosis during implantation window

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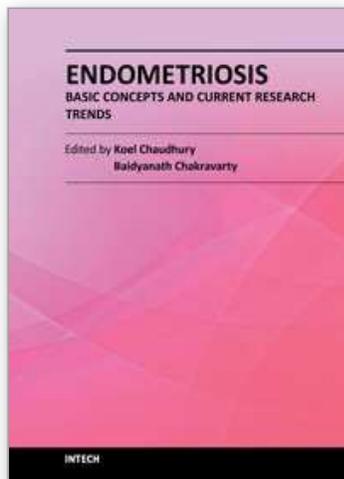
**Endometriosis - Basic Concepts and Current Research Trends**

Edited by Prof. Koel Chaudhury

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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