



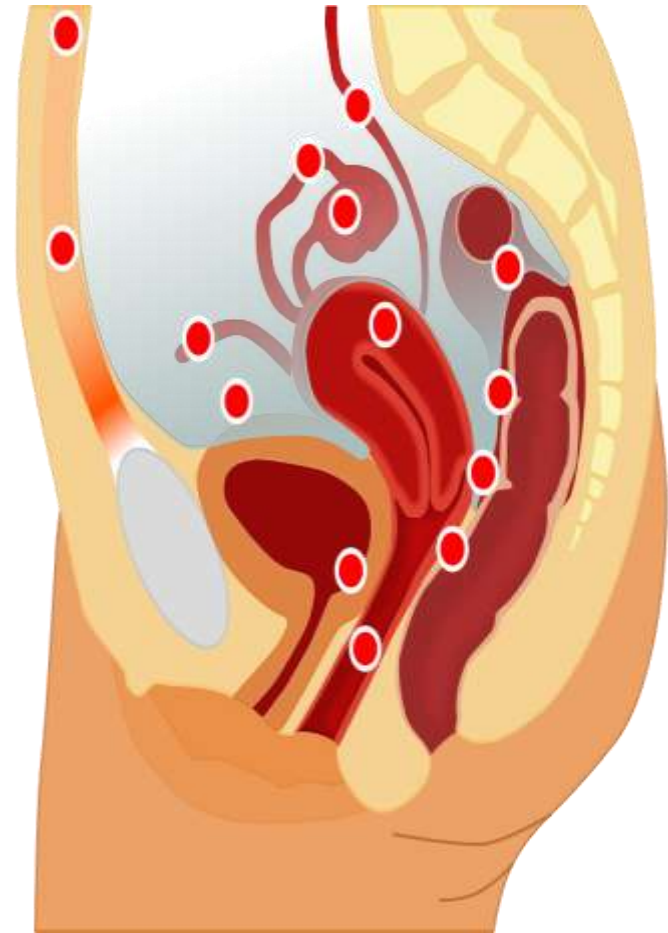
# **New insights into the pathogenesis of endometriosis**

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# Theories of pathogenesis

- Retrograde menstruation (*Sampson's Theory*)
  - Endometrial fragments transported through fallopian tubes at time of menstruation and implanted at intraabdominal sites
- Müllerian (Coelomic) metaplasia (*Meyer's Theory*)
  - Metaplastic transformation of pelvic peritoneum during embryonal organogenesis
- Lymphatic spread (*Halban's Theory*)
  - Substances released/shed from endometrium induce formation of endometriosis





# Theories of pathogenesis

However, since retrograde menstruation is essentially universal, host factors must impact the development of “disease”, such as:

- variations in the ability to “clean up” menstrual debris, probably reflecting immunologic events.
- Genetic differences in the tendency to develop painful conditions
- Medical and psychological co-morbidities



# Theories of pathogenesis

- Three different disease entities:
  - Peritoneal
  - Ovarian
  - Recto-vaginal
- With the current knowledge and understanding of the disease, pathogenesis of endometriosis can be explained by a combination of possible causes rather than a certain theory



# Pathophysiology

- Multifactorial
- Pathogenic mechanisms differ in the formation of distinct types of endometriotic lesions
- Estrogen dependency



# Current concepts

4 areas of basic research:

- 1) Genetics
- 2) Environmental Science
- 3) Cancer Biology
- 4) Immunology



# Genetics

- Genetic predisposition:
  - low progesterone levels may be genetic
  - 10-fold increased incidence in women with an affected first-degree relative
  - Familial clustering in animal model – Rhesus monkeys
- Series of multiple hits within target genes
- Individual genomic changes:
  - Changes in chromosome 10 at region 10q26
  - Changes in the 7p15.2 region



# Environmental factors

- Plastics and cooking with certain types of plastic containers with microwave ovens
- Dioxin exposure - 79% of monkeys developed endometriosis after receiving doses of dioxin
- Pesticides and hormones in our food cause a hormone imbalance
- The risk of endometriosis has been reported to be reduced in smokers (decreased estrogens)





# Dioxin

- Potent chemical toxin
- Reference compound for a large class of halogenated aromatic hydrocarbons
- 95% - incinerators burning chlorinated wastes
  - Dioxin pollution is also affiliated with paper mills, which use chlorine bleaching in their process and with the production of Polyvinyl Chloride (PVC) plastics
- The major sources of dioxin are in the diet:
  - 97.5% - meat and dairy products



# Dioxin

- Experimental endometriosis in Rhesus monkeys shows a dose response relationship
  - Affecting severity of endometriosis
  - Affecting reproductive failure
- Glutathione S-transferase M1 (GSTM1) is responsible for detoxification of dioxin and is a candidate gene for endometriosis development
- Dioxin modulates various hormone receptor systems: estrogen receptor, progesterone receptor, epidermal growth factor receptor and prolactin receptor
- Dioxin shows immunosuppressive activities and is a potent inhibitor of T-lymphocyte function



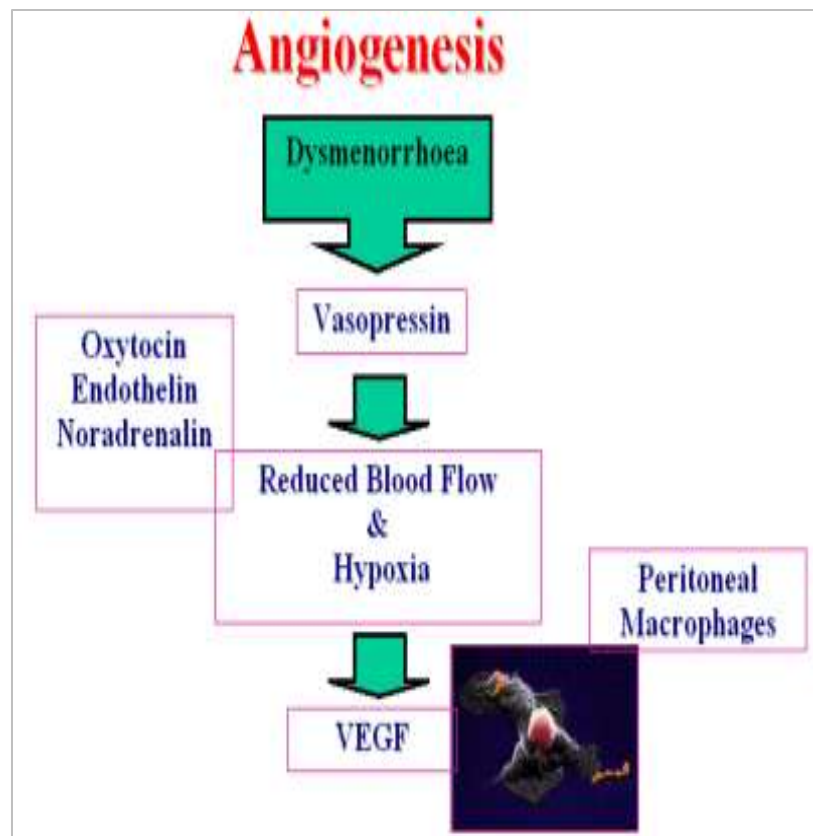
# Cancer biology

- Cellular proliferation and invasion
- T cell mediated invasion may be similar to that which occurs with metastatic neoplasia - immune surveillance systems are inadequate or unable to respond to the seeding tissue
- Accumulation of various growth factors and the occurrence of angiogenesis to produce a self contained blood supply are the features that implicate the relationship of cancer biology and ectopic endometriotic tissue development.



# Angiogenesis

- The endometrium of women with endometriosis has an increased capacity to proliferate, implant and grow in the peritoneal cavity
- May enter a blood or lymph vessel and disseminate to distant body sites
- Endometrium is a rich source of growth factors which promote angiogenesis including the fibroblast growth factors, FGF1 and FGF2 and the vascular endometrial growth factor (VEGF)





# Extracellular Matrix Remodeling

- Matrix metalloproteinases (MMP) are responsible for extracellular matrix and endometrium remodeling
- Suppression of MMP inhibits establishment of ectopic lesions by human endometrium
- MMP-1 expression is correlated with the activity of endometriotic tissue suggesting its involvement in tissue remodeling and reimplantation of endometriotic lesions
- Specific cell adhesion receptors and their extracellular matrix ligands are being investigated to understand the invasive features of endometriosis: 4 major groups: cadherins, selectins, members of immunoglobulin superfamily and integrins



# Apoptosis

- Programmed cell death is impaired in endometriosis
- Decreased apoptosis in endometriosis cells may help an activated immune system to establish ectopic foci of disease



# Immunologic dysfunction

- Altered immune response to the displaced endometrial tissue
- Increased humoral immune responsiveness and macrophage activation
- Diminished cell-mediated immunity with decreased T-cell and natural killer cell responsiveness
- Humoral antibodies to endometrial tissue have also been found in sera of women with endometriosis (autoantibodies)



# Altered macrophage function

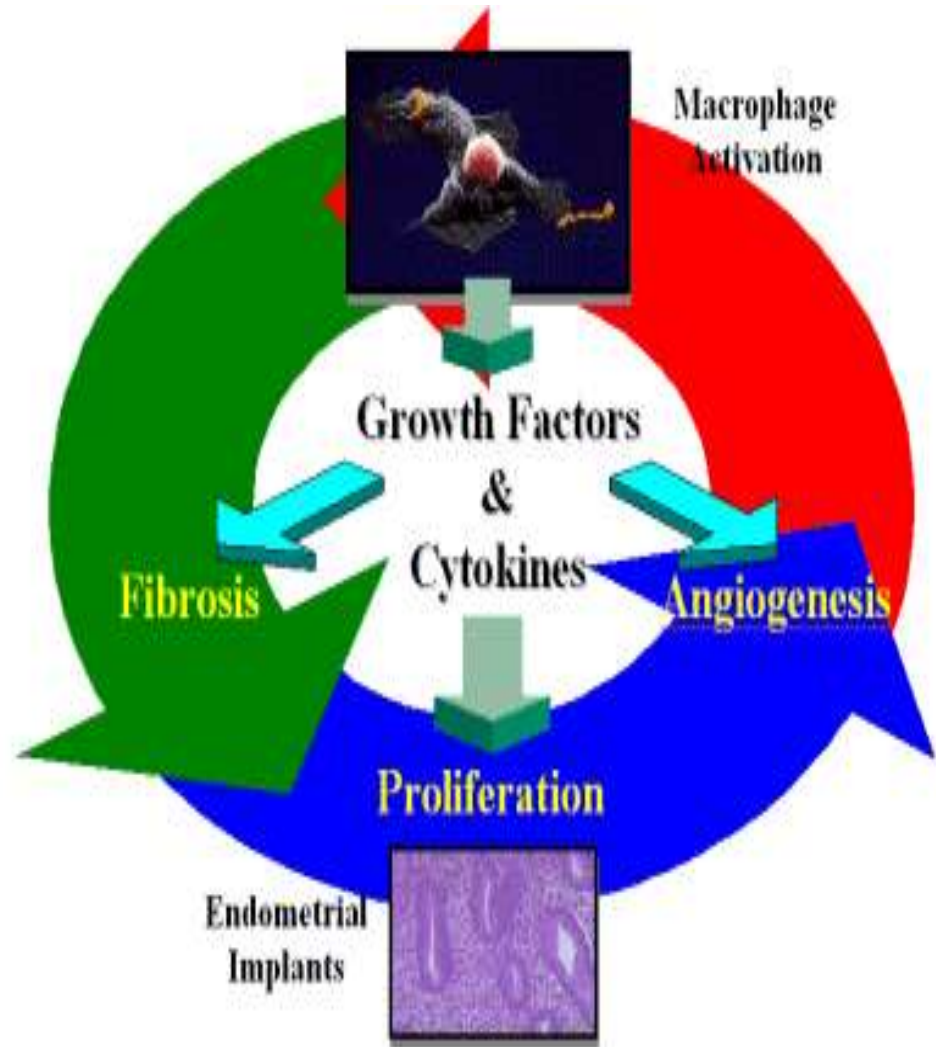
- Macrophages secrete high concentration of substances such as growth factors that restrict natural killer activity, increase angiogenesis and fibrosis and induce endometrial cell proliferation in vitro
- These changes in peritoneal milieu could also be responsible for the failure of fertilization, embryo development and implantation





# Paracrine changes in peritoneal fluid

- Macrophage derived substances such as prostanooids, cytokines, growth factors and angiogenic factors have been detected in the peritoneal fluid of women with endometriosis





# Paracrine changes

- Interleukin 8 (IL-8) is a chemoattractant and activating factor for human neutrophils and a potent angiogenic agent:
  - IL-8 concentrations in correlation with disease stage
  - Peritoneal macrophages play an important role in the initiation of the pathogenic cascade as sources of IL-1 and TNF- $\alpha$  in addition to IL-8
- Monocyte Chemotactic Protein-1 (MCP-1)
  - Level significantly higher in patients with severe disease
  - Directly stimulating endometrial cell proliferation
- VEGF is a growth factor related to angiogenesis and released in response to hypoxia
  - Association between the retrograde menstruation and /or dysmenorrhoea and changes in peritoneal fluid
  - Activated macrophages in the peritoneal cavity produce large amount of VEGF

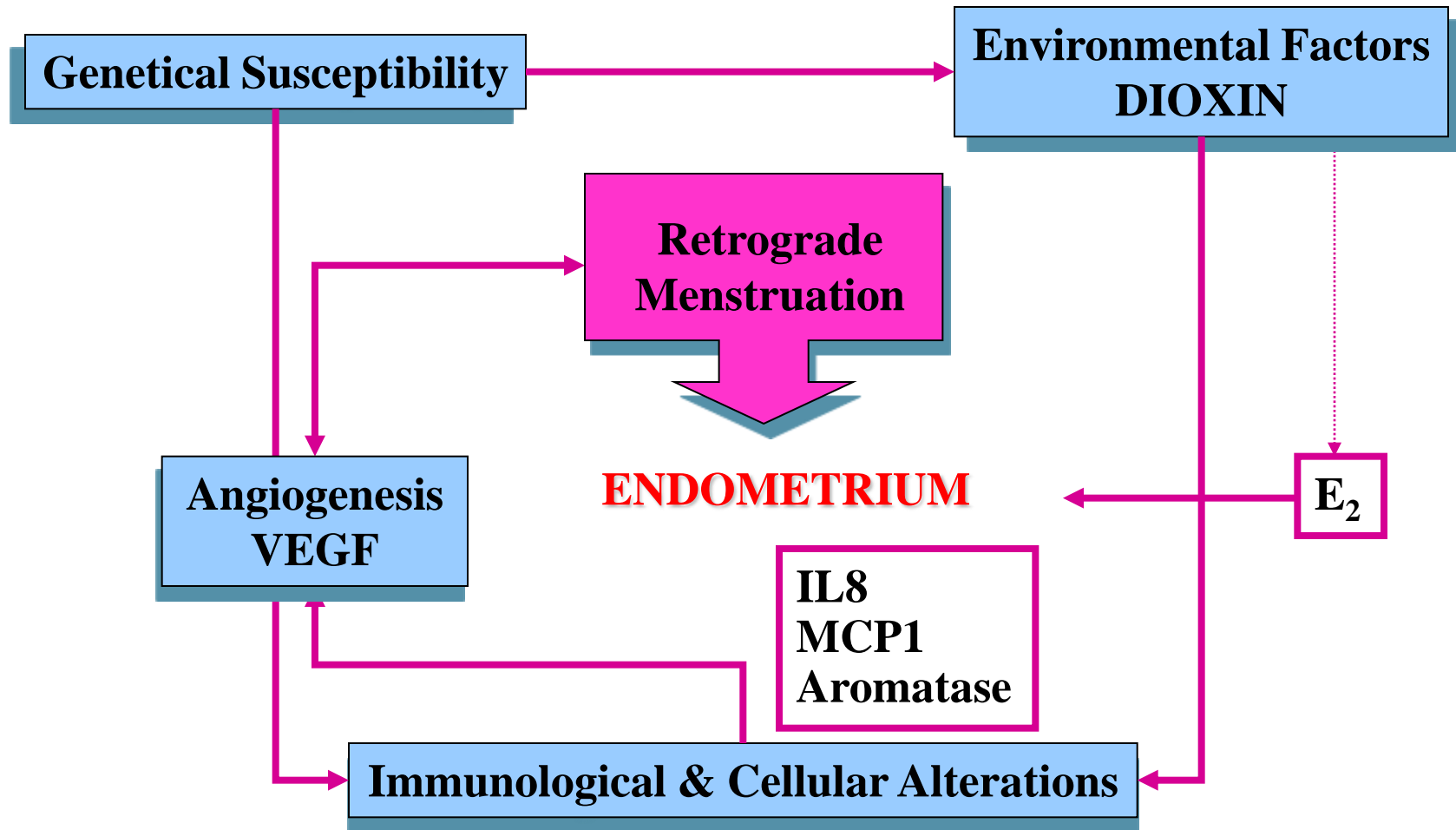


# Summary of pathogenesis

- Multifactorial disease:
- Interaction between multiple gene loci and environment
- Causes of immune or inflammatory deficiency may be related to the effects of stress on immune functioning, or may be genetically determined
- Environmental factors such as Dioxin may be responsible for immunosuppressive activities and altered tissue specific responses to hormones
- Chronic immunosuppression in combination with altered hormonal regulation may facilitate aberrant growth of endometrial tissue in the peritoneum
- The mechanism appears to require endometrium and retrograde menstruation in most cases of disease



# Pathogenesis





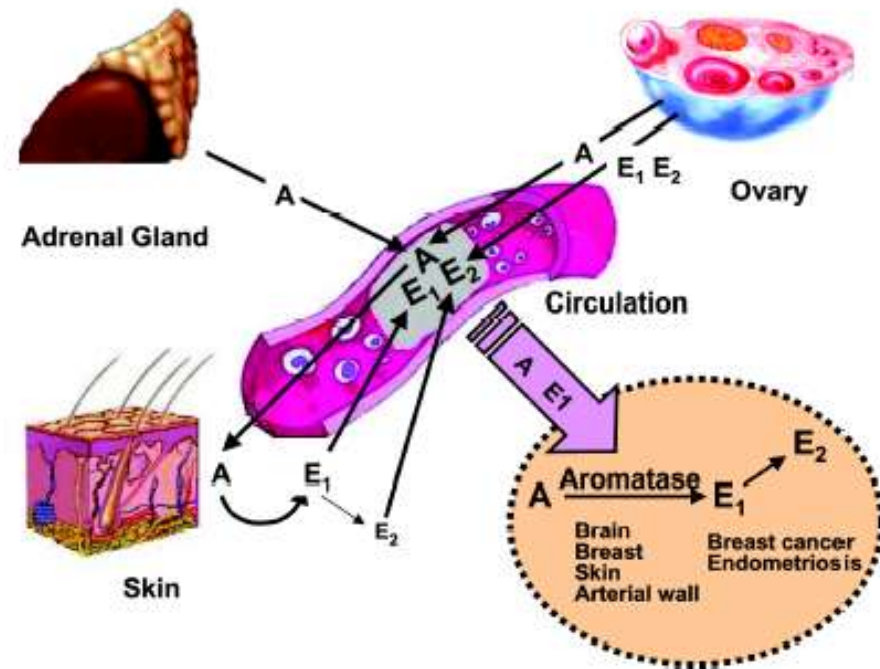
# Future directions

- Aromatase inhibitors
- Selective Progesterone Receptor Modulators
  - RU486 (mifepristone)
- GnRH antagonists
- TNF- $\alpha$  inhibitors
  - Pentoxifylline, Infliximab
- Angiogenesis inhibitors
  - Cabergoline, thalidomide, VEGF inhibitors
- MMP inhibitors
- Immunomodulators
- Estrogen receptor- $\beta$  agonists



# Aromatase inhibitors - AI

- Suppression of the physiological conversion of androgens to estrogens
- Aromatase enzyme has been demonstrated locally in endometriotic implants and a molecular etiology of endometriosis has been proposed
- AI effective in pain reduction similar to GnRHa
- Possible second line treatment



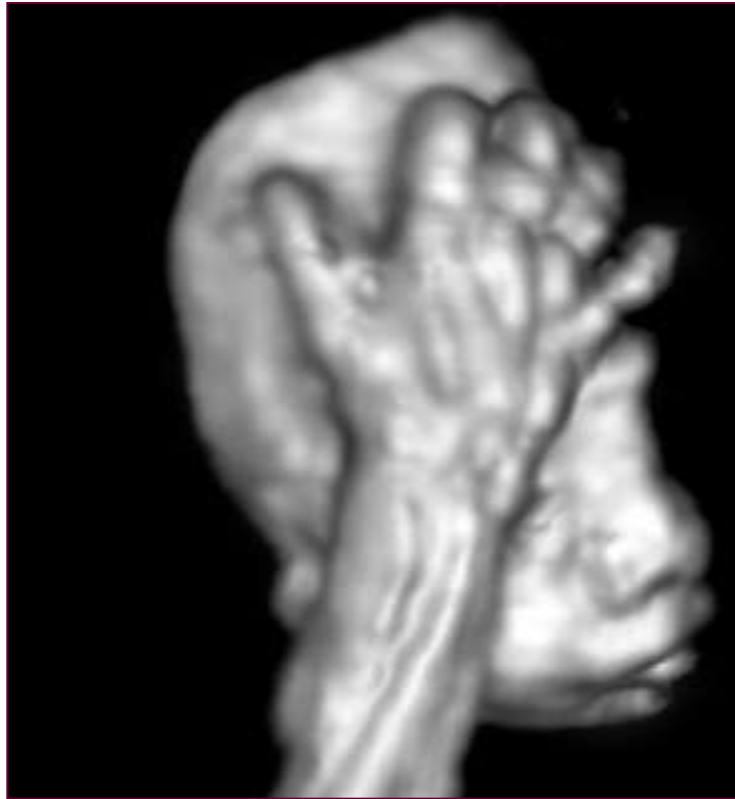


# Complementary therapies

- Acupuncture
  - Cochrane - evidence of effectiveness without side effects
- TENS – short term management
- Traditional Chinese Medicine – TCM
- Vitamins B1, B6, E
- Magnesium
- Topical heat - no evidence
- Spinal manipulations – no evidence
- Behavioral interventions



# Thank you



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