# Role of risk factors in the development of endometriosis

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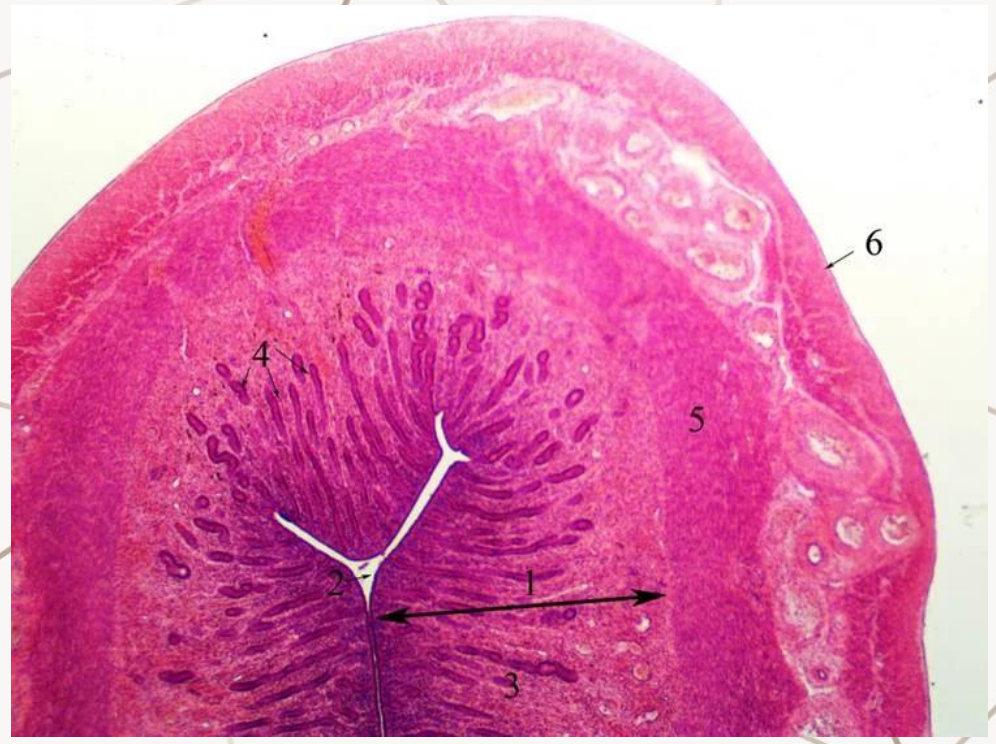
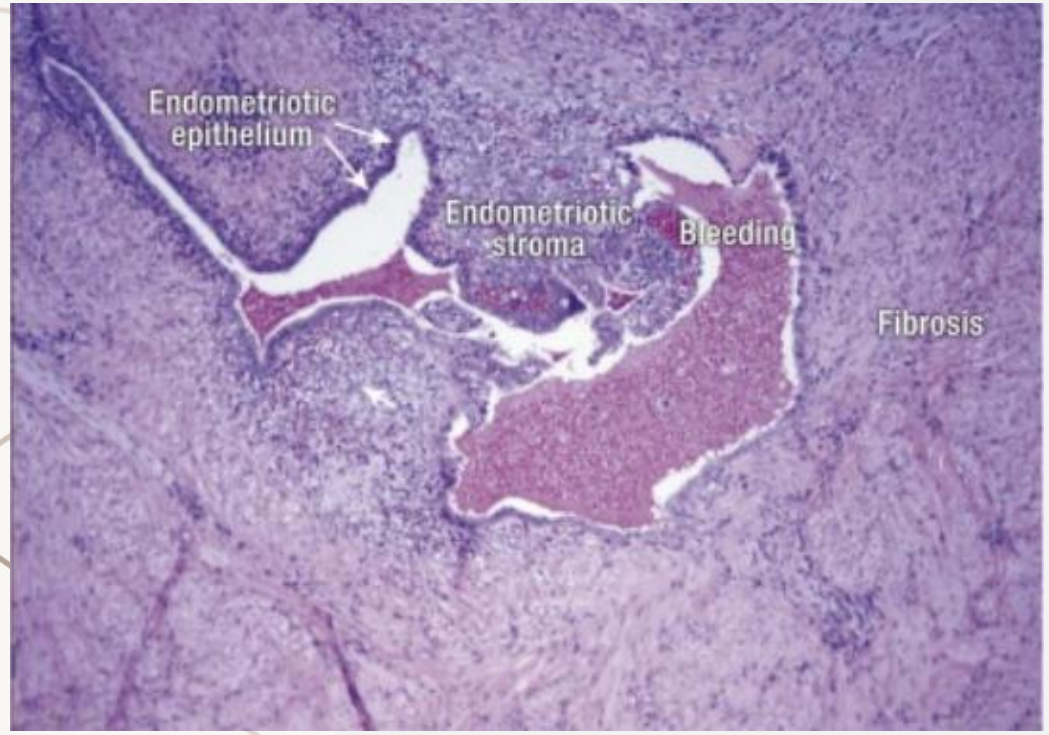
**Endometriosis** is an estrogen-dependent inflammatory disorder of the endometrium that is characterized by the presence of functionally active endometrial tissue, stroma and glands outside the uterine cavity.

The disease may also affect the bladder, bowel (most commonly the rectum and appendix), deep pelvic nerves, ureters, anterior abdominal wall, abdominal skin, diaphragm, pleura, lungs, pericardium, and brain.

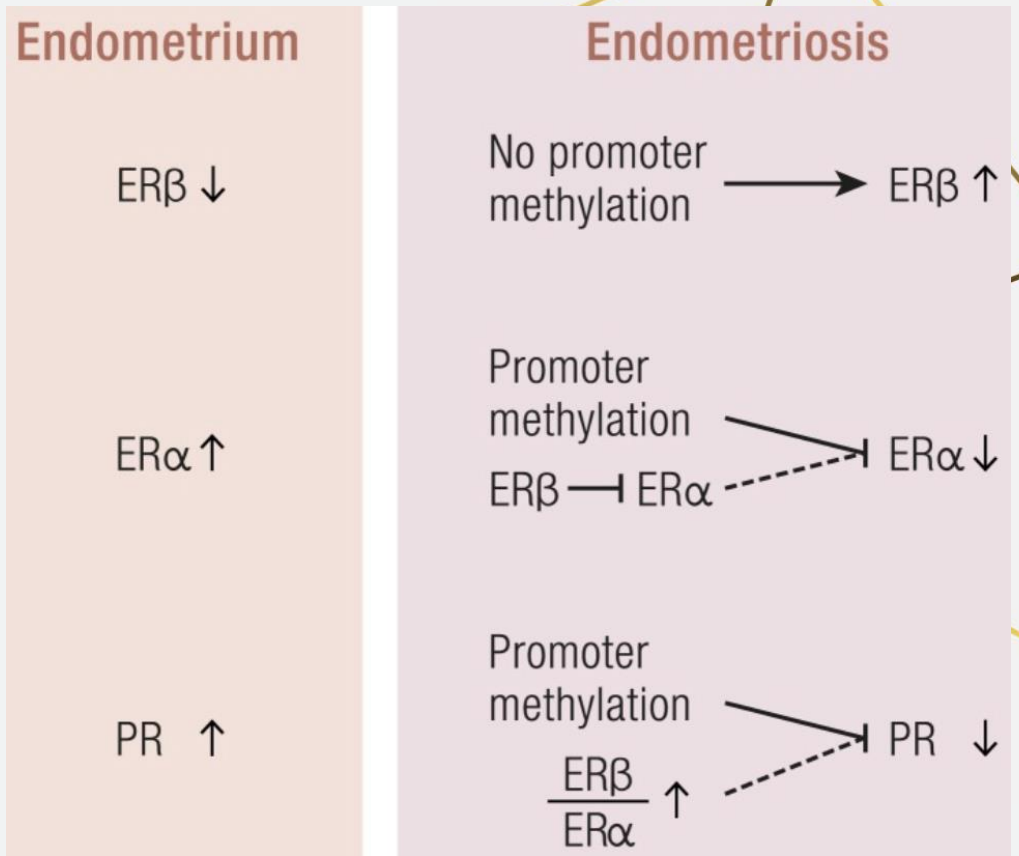


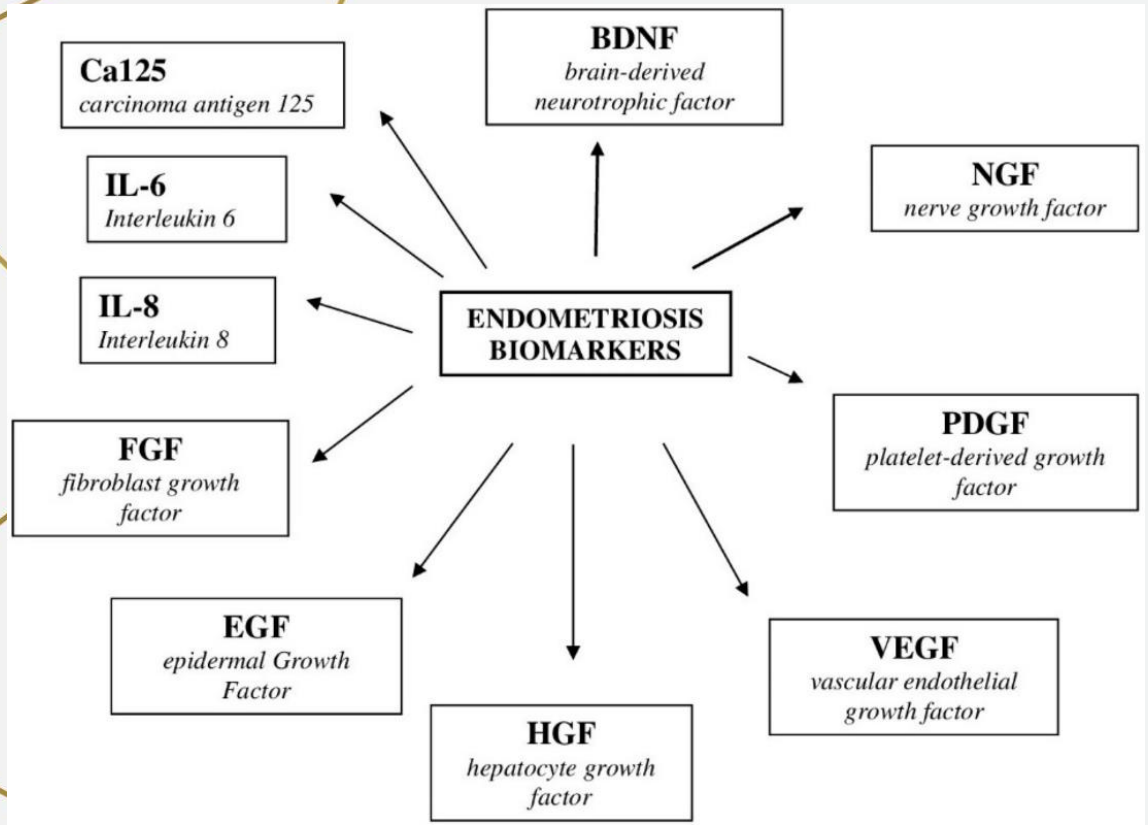

Normal uterus tissue




Peritoneal endometriosis with fibrosis

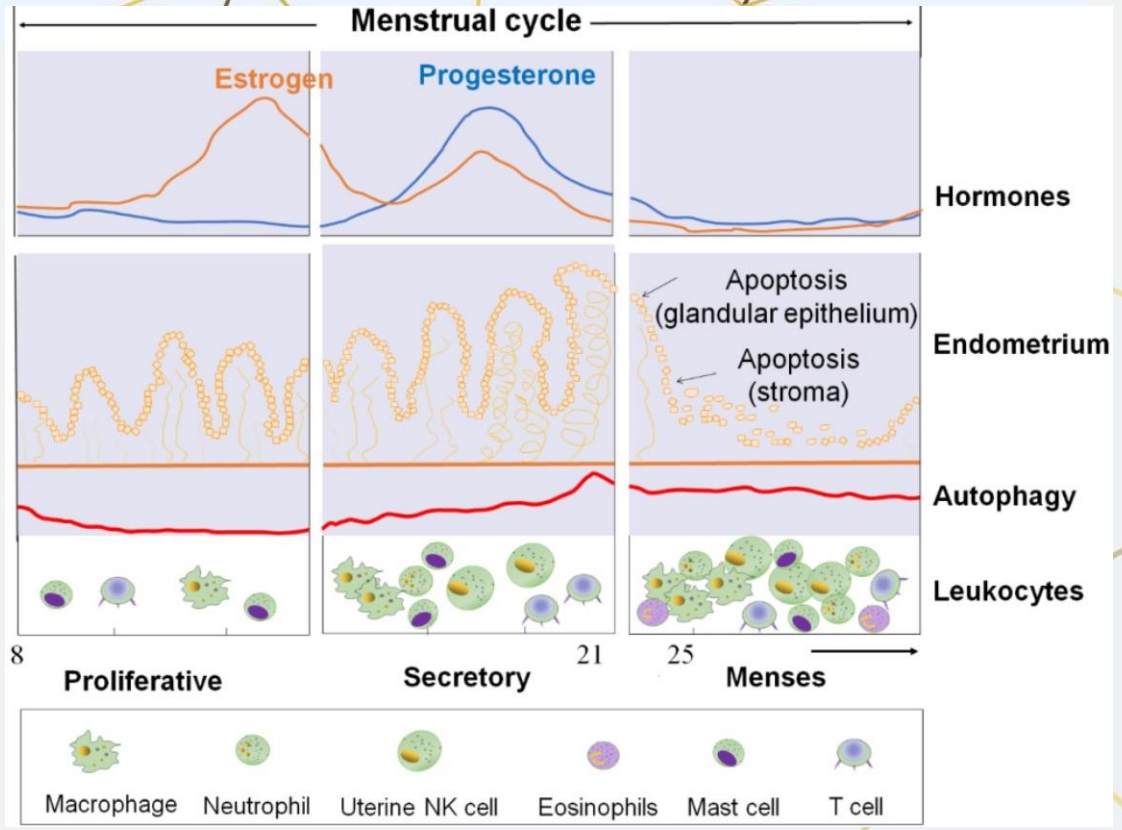
Biomarkers obtain from serum, plasma or urine, in order to a quick and simple diagnosis. GATA6 blocks hormone sensitivity, represses GATA2, and induces markers of endometriosis when expressed in healthy endometrial cells.



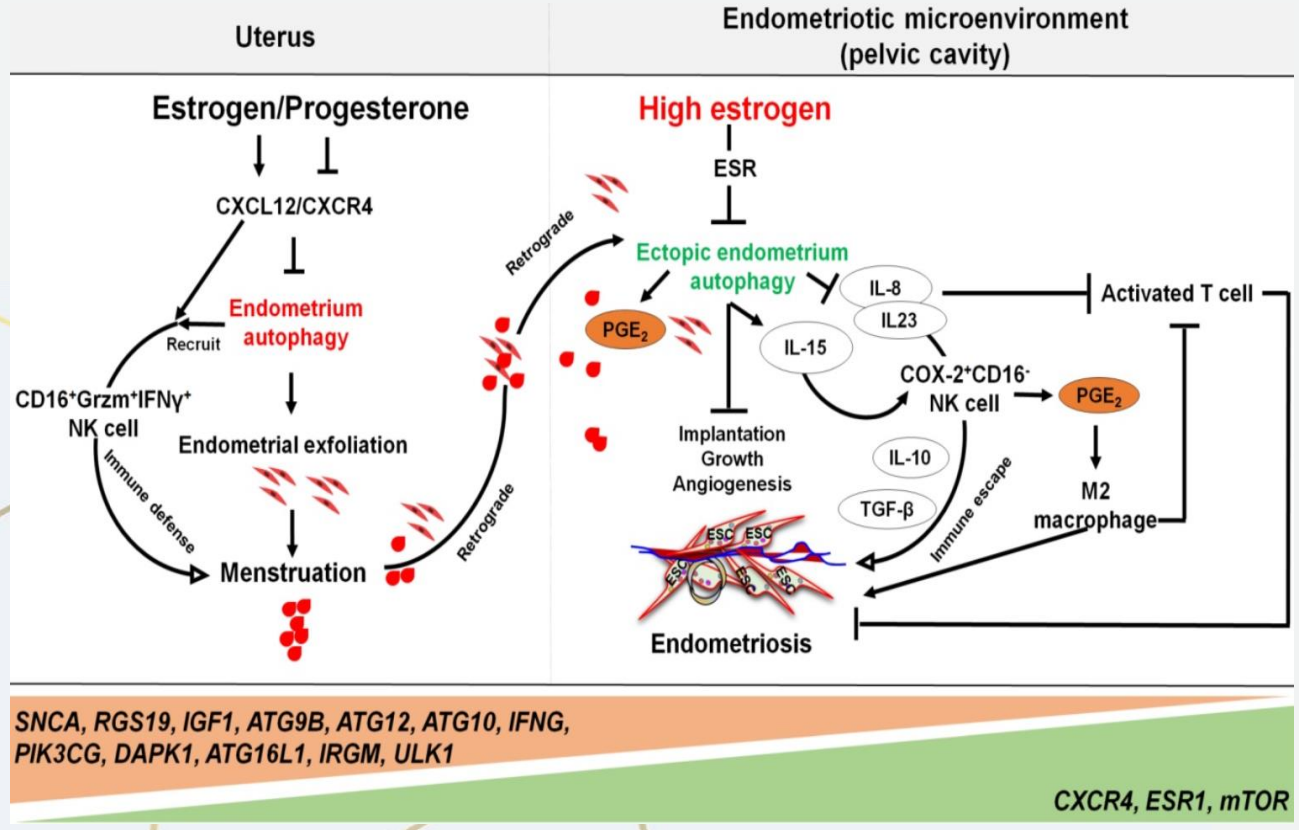




The marker of endometriosis was sought among growth factors and cytokines, because the development of ectopic implants is accompanied by the processes of invasion, proliferation and angiogenesis.

# Normal regulation

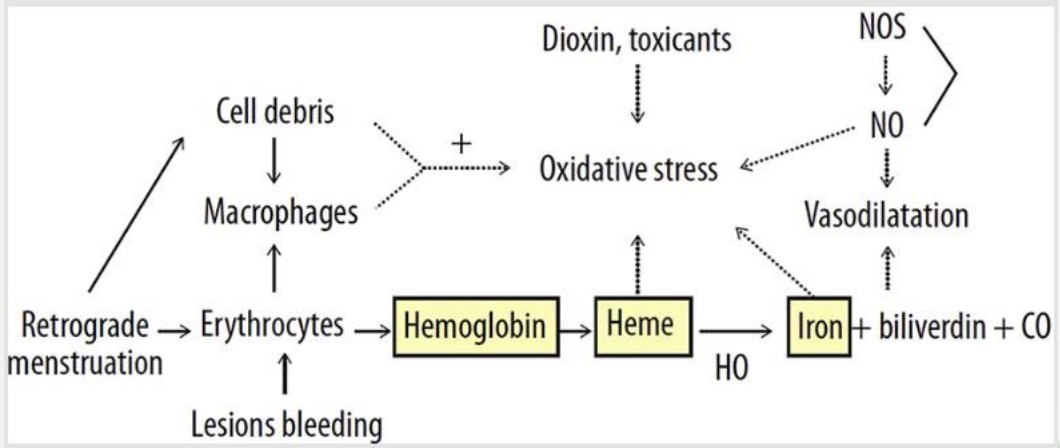



# Abnormal regulation



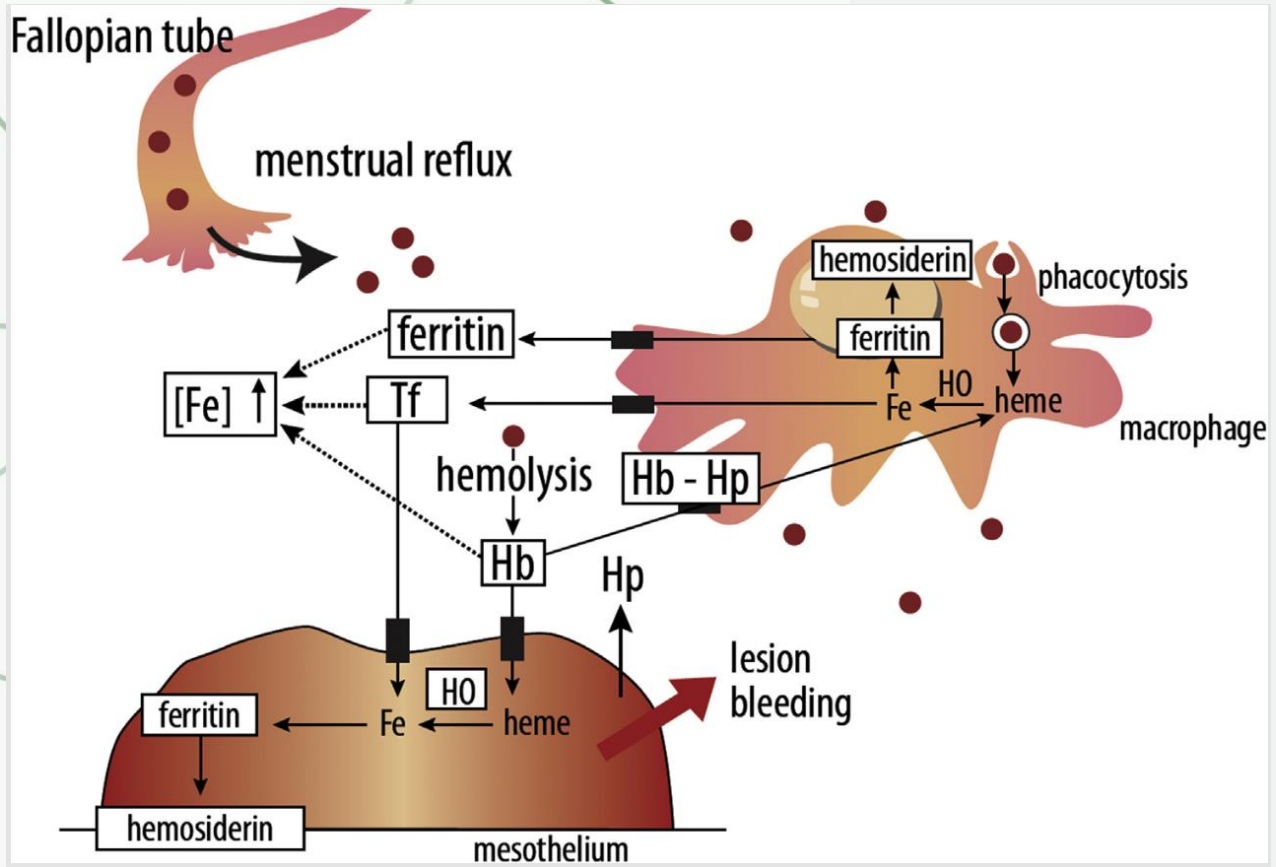

In the presence of high concentrations of estrogen and progesterone resistance, however, autophagy-related genes (e.g., SNCA, RGS19, IGF1 ATGs, CXCR4, ESR1, and mTOR) are altered, leading to decreased endometrial autophagy. The suppression of endometrium autophagy directly accelerates the implantation, growth and angiogenesis of endometriotic lesions, whilst promoting the immune escape of endometriotic lesions through IL-8 and IL-23-mediated COX-2+CD16-NK cell differentiation. Therefore, the effects of aberrant ovarian steroid hormones-autophagy-immunity axis contribute to the occurrence and development of endometriosis.

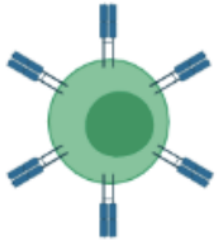
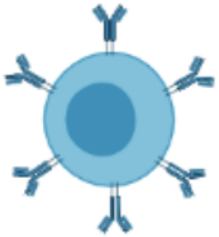
| Immune Factor | Role in Endometriosis |
|---|---|
| TNF-α | Increasing vascular permeability and transformation of inflammatory factors in the peritoneal cavity, which exacerbate peritonitis. |
| NF-κB | Controlling gene expression associated with immune response, cellular proliferation, and cytokine production. |
| MCP-1 | Stimulation of monocytes to migrate from peripheral blood to the peritoneal cavity to turn into macrophages, leading to local inflammation. |
| IL-1β | Induction of VEGF and COX-2 expression leading to the progression of endometriosis. |
| IL-6 | In the tide to impair the function of NK cells (natural *killer*) by regulating the protein expression of tyrosine phosphatase (SHP-2) in endometriosis. |
| IL-10 | In a mouse model with induced endometriosis, inhibition of IL-10 activity was found to be helpful in reducing lesions. |
| IL-15 | Endometriotic cells in patients with endometriosis show higher concentrations of this cytokine in endometrial patients . |
| IL-16 | Higher concentrations of IL-16 in women with endometriosis are associated with the development of the disease by stimulating the secretion of IL-6, TNF-α and IL-1β. IL-16 polymorphisms are associated with women's susceptibility to the development of endometriosis and its severity. |
| IL-17A | In endometriosis, IL-17A is expressed in endometrial lesions, and therefore the inflammatory environment of the peritoneal cavity of patients with endometriosis may be associated with the production of IL-17A . |
| IL-18 | IL-18 regulates the production of TNF-α and IL-8, acts as a potent angiogenic factor, and also regulates the intercellular expression of adhesion molecule 1 through NFκB and may increase MMP production. |
| IL-27 | IL-10 + Th17 stimulate the proliferation and implantation of ectopic lesions and accelerate the progression of endometriosis, making IL-27 a key regulator in endometriotic lesions. |
| IL-33 | Member of the IL-1 family. IL-33 induces the synthesis of Th2-type cytokines through its orphan receptor ST2. |
| IL-37 | Increased levels of IL-37 expression in eutopic and ectopic endometrium in women with stage III-IV ovarian endometriosis may be involved in inflammatory processes leading to endometriosis . |




An important defense mechanism to counteract the effects of hemorrhage is mediated by haptoglobin (Hp), which binds extracellular Hb, thereby attenuating its oxidative and inflammatory potential. Haptoglobin also promotes clearance of Hb via the CD163 scavenger receptor present on macrophages.

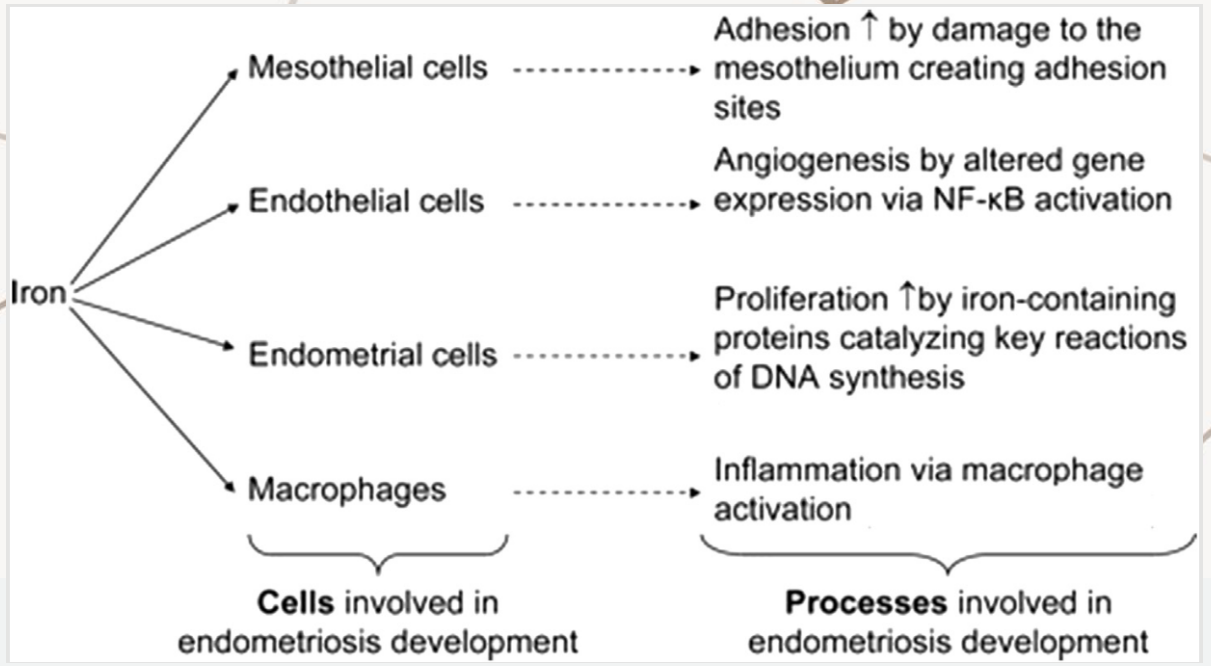
Macrophages usually phagocytose senescent erythrocytes or endocytose the Hb–Hp complex. Metabolism of Hb and heme by heme oxygenase (HO) releases iron, which is then incorporated into ferritin in macrophages or returned to the iron transporter transferrin (Tf) via the peritoneal fluid. Cellular iron storage within ferritin limits the capacity of iron to generate free radicals and confers an antioxidant effect. Increased pelvic iron concentrations result from transporter transferrin , ferritin, and Hb accumulation in peritoneal fluid. Transferrin and Hb may be assimilated by ectopic endometrial cells, resulting in the formation of iron deposits (ferritin or hemosiderin) inside lesions.

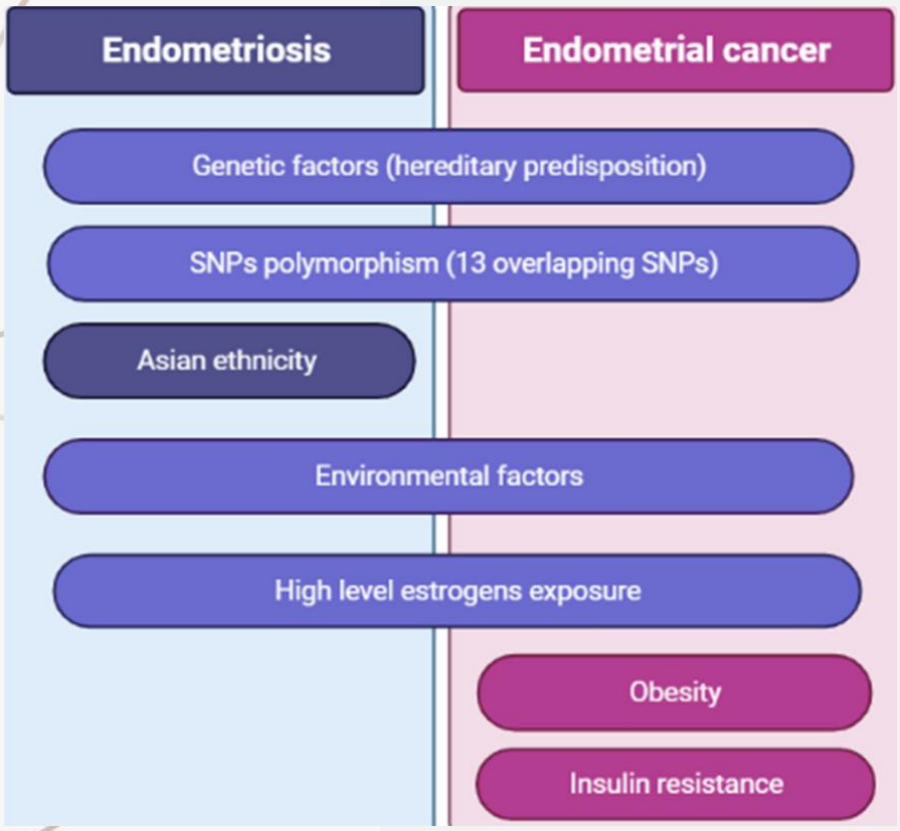


| | Macrophages | Neutrophils | NK Cells | T Cells | B Cells |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| **Immune Dysregulation** | • High numbers in PF and endometriotic lesions<br>• ↓ phagocytosis<br>• ↑ cytokine secretion (TNF-α, IL-6, IL-1β, NF-κB, VEGF)<br>• Altered phenotype: more proinflammatory | • Elevated numbers in PF<br>• Preconditioned by bacterial presence<br>• Recruited to lesions by IL-8 | • Impaired by aberrant immune environment (IL-6, TGF-β)<br>• Altered activating/ inhibitory receptor pattern | • Altered subset proportions<br>• ↑ $T_H2$ ↑ $T_H17$<br>• Increased IL-17 secretion | • Produce anti-endometrial autoantibodies<br>• ↑ IL-6 ↑ IL-17 |
| **Implications on Endometriosis** | • ↓ ability to eliminate refluxed endometrial tissue<br>• Promote further immune activation and inflammation<br>• Lesion growth & vascularization | • Involved in early lesion formation<br>• Promote angiogenesis | • Reduced cytotoxic capacity =<br>• ↓ immunosurveil-lance<br>• Lesion survival | • Suppressed cell-mediated immunity = ↓ immunosurveil-lance<br>• Stimulate production of proinflammatory cytokines and pro-angiogenic factors<br>• Endometriosis progression | • Contribute to inflammation, disease progression<br>• Role is unclear |

# Risk Factors for Endometriosis Include:

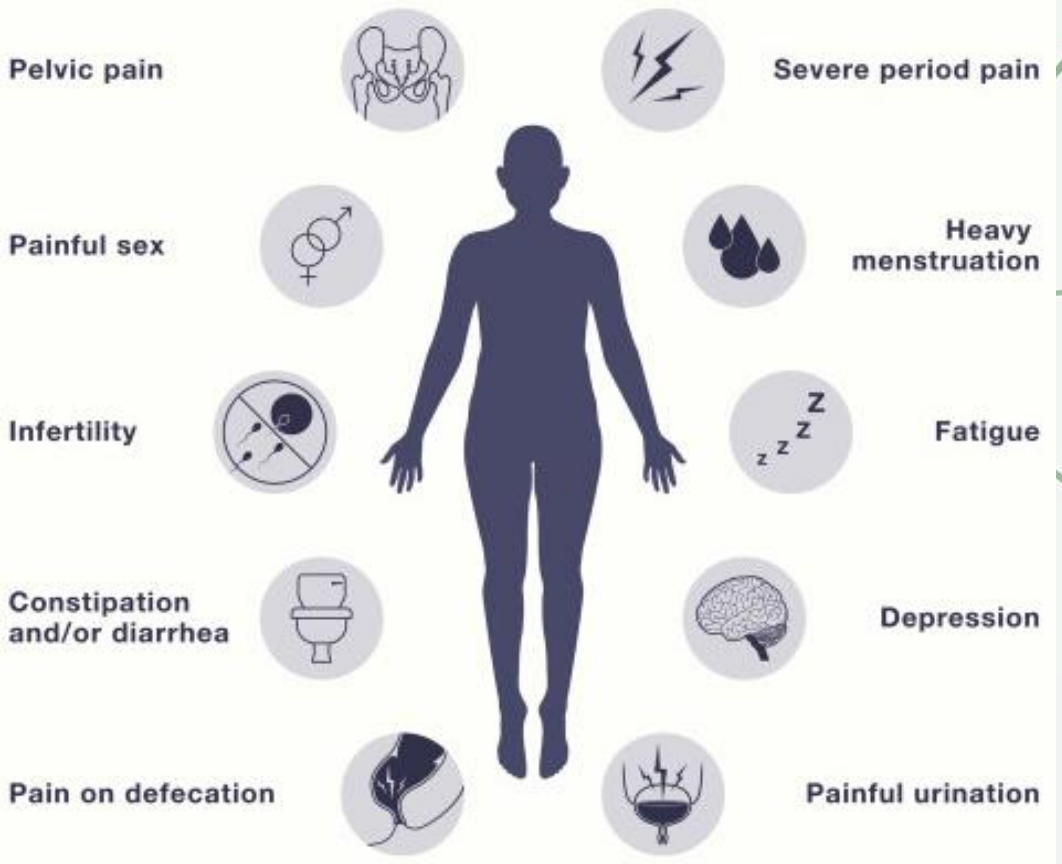
•Early menarche (before the age of 11);
•Shorter than 27-day genital cycles, genital defects, including hymen overgrowth or narrowing of the cervical canal;
•Endometriosis is more often diagnosed in infertile women who are active smokers and whose body mass index is normal or low;
•Imbalance between physical activity and rest;
•Nutrition (unsaturated/trans-unsaturated fats more than green vegetables and fresh fruits);
•Daily consumption of alcohol in the amount of at least 10 g per day;



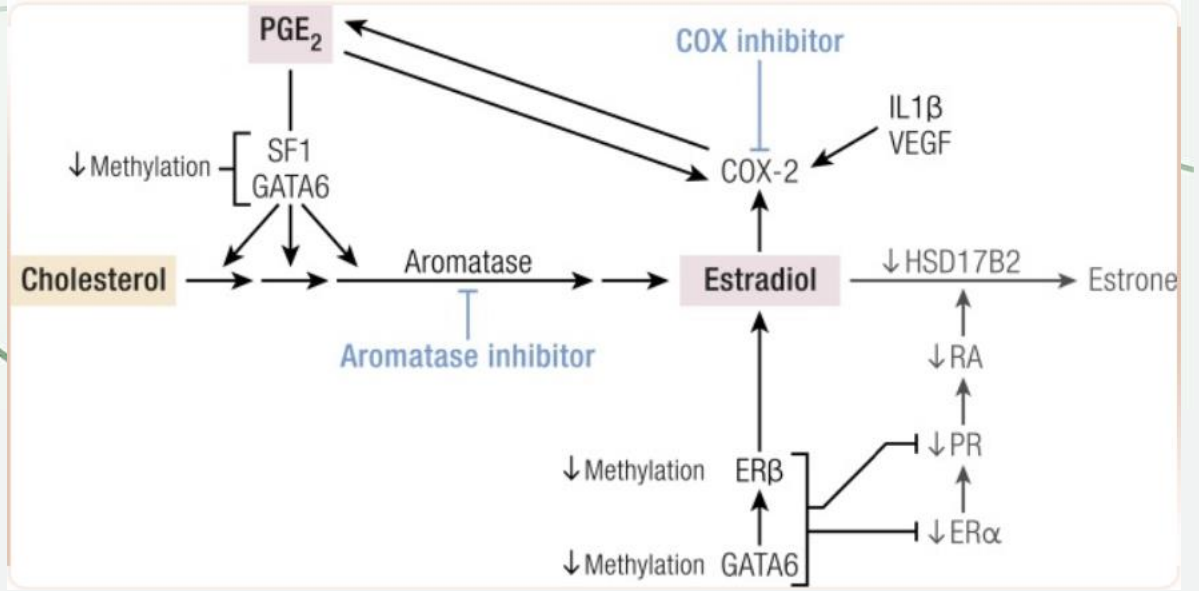




•Low BMI (obesity is also a risk factor for severe dysmenorrhea);
•Small number of births;
•Asian race;
•Age 25–29;
•Environmental pollution;
•Uterine outlet obstruction;
•Transverse vaginal septum or imperforate hymen.

Red meat characterized by a high content of dioxins, hormones and fat, increasing the concentration of estrogens. Green vegetables and fresh fruits contain antioxidants, which play an important role in the proper functioning of the immune system and the removal of free radicals. Environmental factors such as elevated levels of phthalate esters, persistent organochlorine pollutants, perfluorochemicals, and exposure to cigarette smoke can increase risk of developing endometriosis by inducing oxidative stress, altering hormonal homeostasis, or by changing immune responses. Tobacco may alter aromatase as well as increase the body's inflammatory response. Maternal exposure to diethylstilbestrol (DES) has been associated with a greater risk of endometriosis in female offspring.

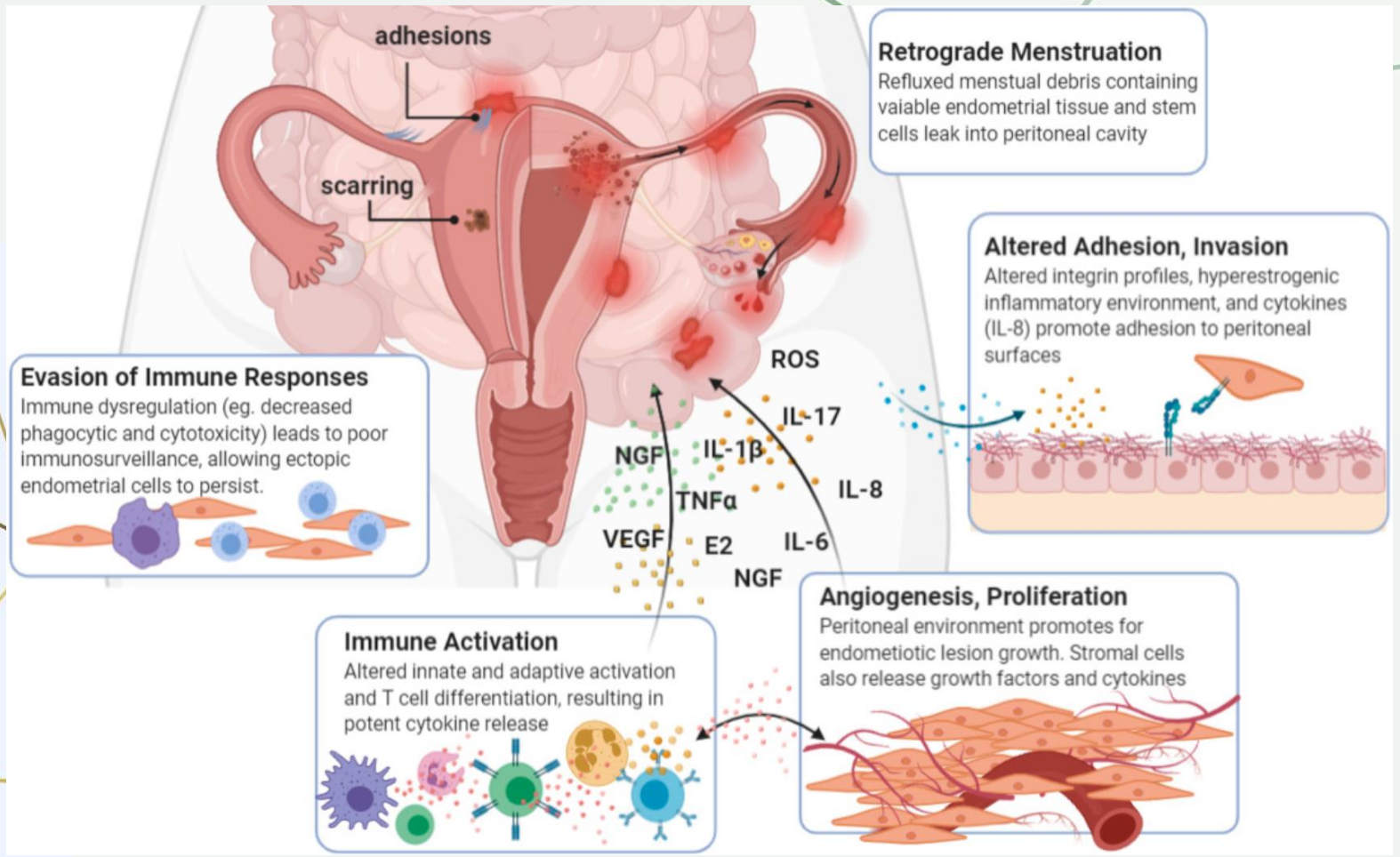



Omega-6 fatty acids derived from the diet are the precursors of the proinflammatory prostaglandins E2 and F2α that probably increase uterine cramps and cause the painful symptoms. However, prostaglandins E3 and E3α derived from the Omega-3 fatty acids were linked to reduced inflammation and thus, lesser pain.



# Conclusion

The main mechanisms of developing endometriosis are inflammation and oxidative stress, which reduce immune reactviti and  hormone syntesis. All risk factors impact on different elements of our organism via cellular, molecullar and genetic changes. That’s why maintaining a healthy lifestyle is so important.



Thank you for your attention!