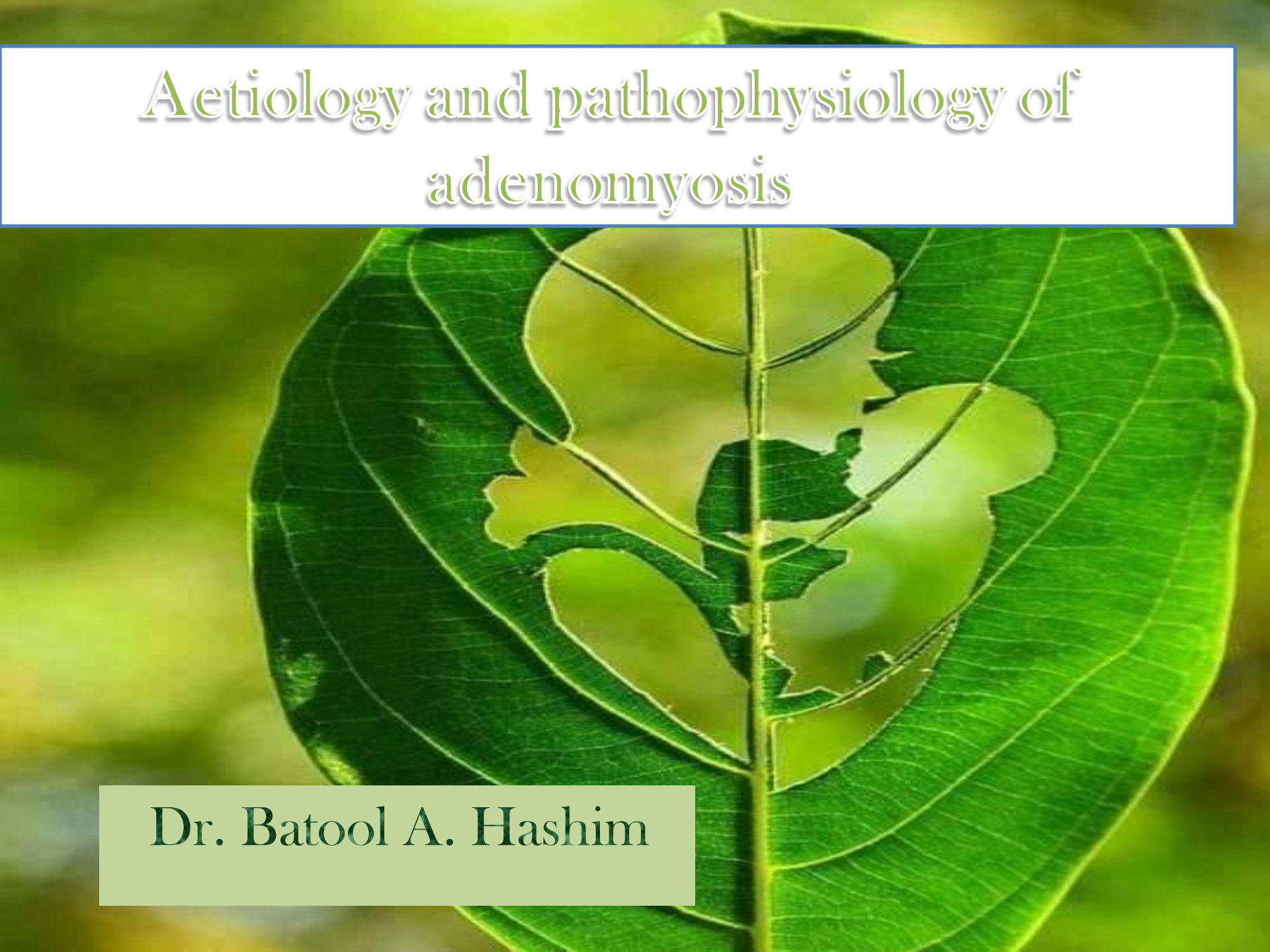

بسم الله الرحمن الرحیم

Aetiology and pathophysiology of adenomyosis



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introduction

- In addition to well proved association of adenomyosis with
- Dysmenorrhea
- abnormal uterine bleeding
- dyspareunea
- there is increasing evidence that adenomyosis constitutes an important factor of infertility.

But this symptomatology is not specific and may overlap with other gynecological diseases like endometriosis and leiomyomas that adenomyosis may frequently coexist with, Therefore, the elucidation of its pathophysiology is of utmost clinical importance.

- Various theories about the etiopathogenesis of adenomyosis have been proposed so far.
- However, the exact cause is still unknown.
- **invagination of endometrium into the myometrium.**
- **Adenomyosis develops *de novo from embryologic* misplaced pluripotent Mullerian remnants.**
- **invagination of the basalis proceeds along the intramyometrial lymphatic system, leading to adenomyosis.**
- **Adenomyosis originates from bone marrow stem cells that are displaced through the vasculature**
- **Steroid hormones have also been emphasized in the pathogenesis**
- **The P۴۵۰ aromatase protein was localized in adenomyotic glands and mRNA for aromatase CYP۴۵۰ was localized in adenomyotic tissue homogenate as well**
- **estrone sulfatase may be involved in the pathogenesis**
- **altered ۱۷β-hydroxysteroid dehydrogenase type ۲ in the endometrium in women with adenomyosis**

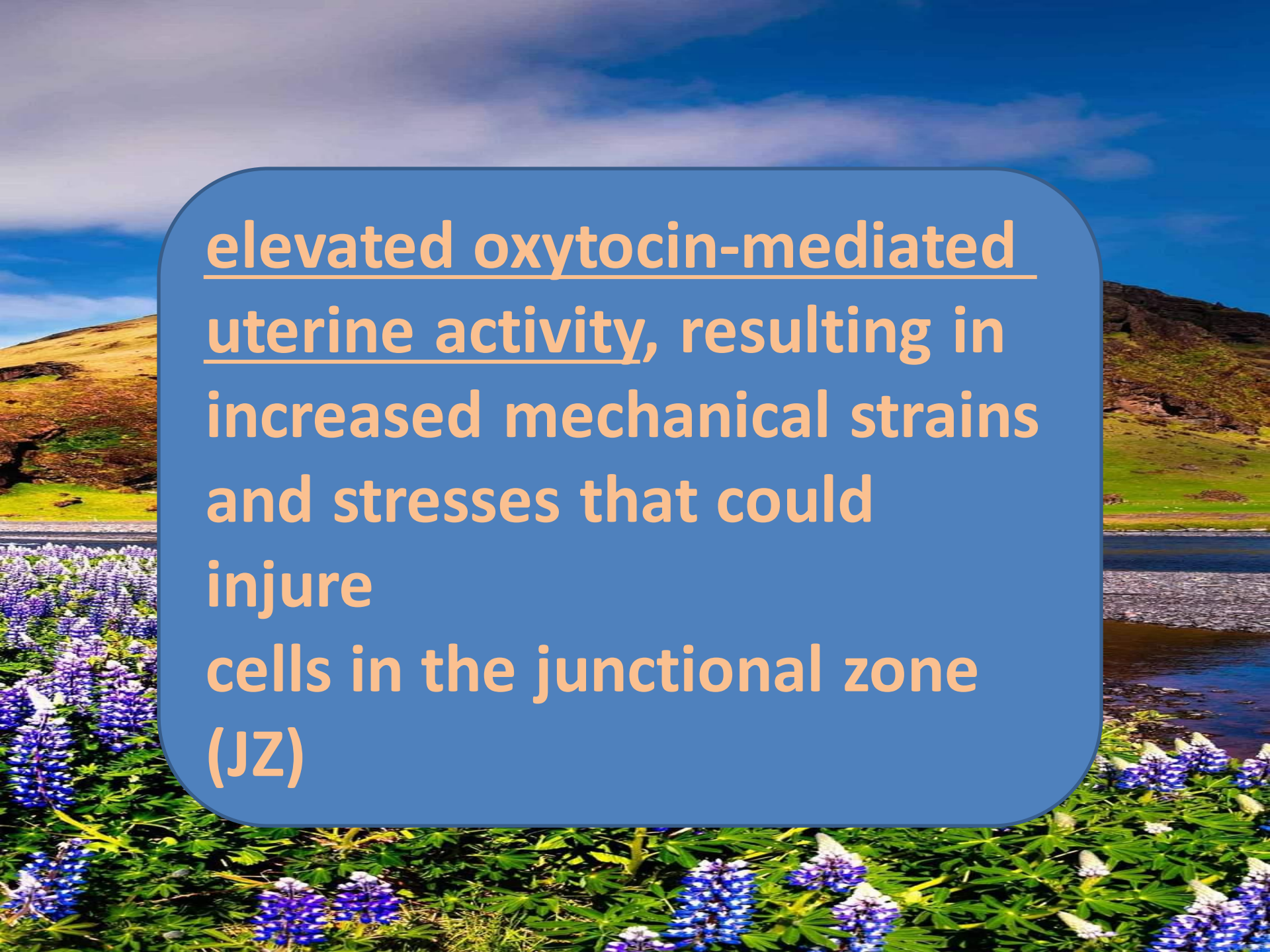
two main theories have been proposed in the literature:

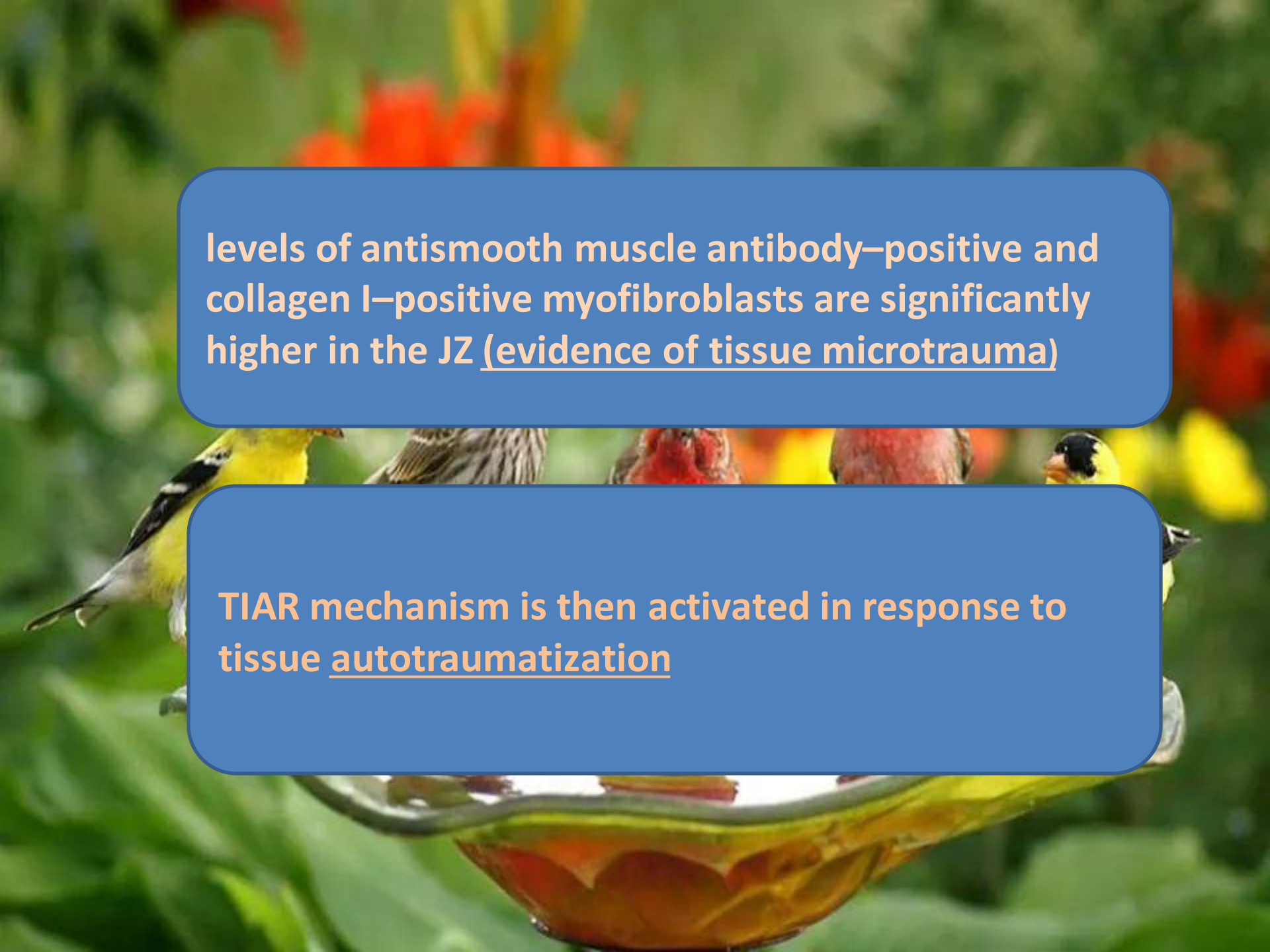
- invagination of the endometrial basalis as a result of activation of the tissue injury and repair (TIAR) mechanism
- metaplasia of displaced embryonic pluripotent Mullerian remnants or differentiation of adult stem cells.


supraphysiological estrogen
production (hyperestrogenism)
(local paracrine activity)in the
eutopic and ectopic endometrium of
patients with adenomyosis

Reduced conversion of E٢ to the less potent estrone was also observed in the eutopic and ectopic endometrium of patients with adenomyosis, as a consequence of decreased expression of ١٧-b hydroxysteroid dehydrogenase type ٢ (١٧-b HSD٢) enzyme

loss of progesterone action and finally a **mechanism of P resistance fostering abnormal endometrial proliferation.**


elevated oxytocin-mediated uterine activity, resulting in increased mechanical strains and stresses that could injure
cells in the junctional zone (JZ)

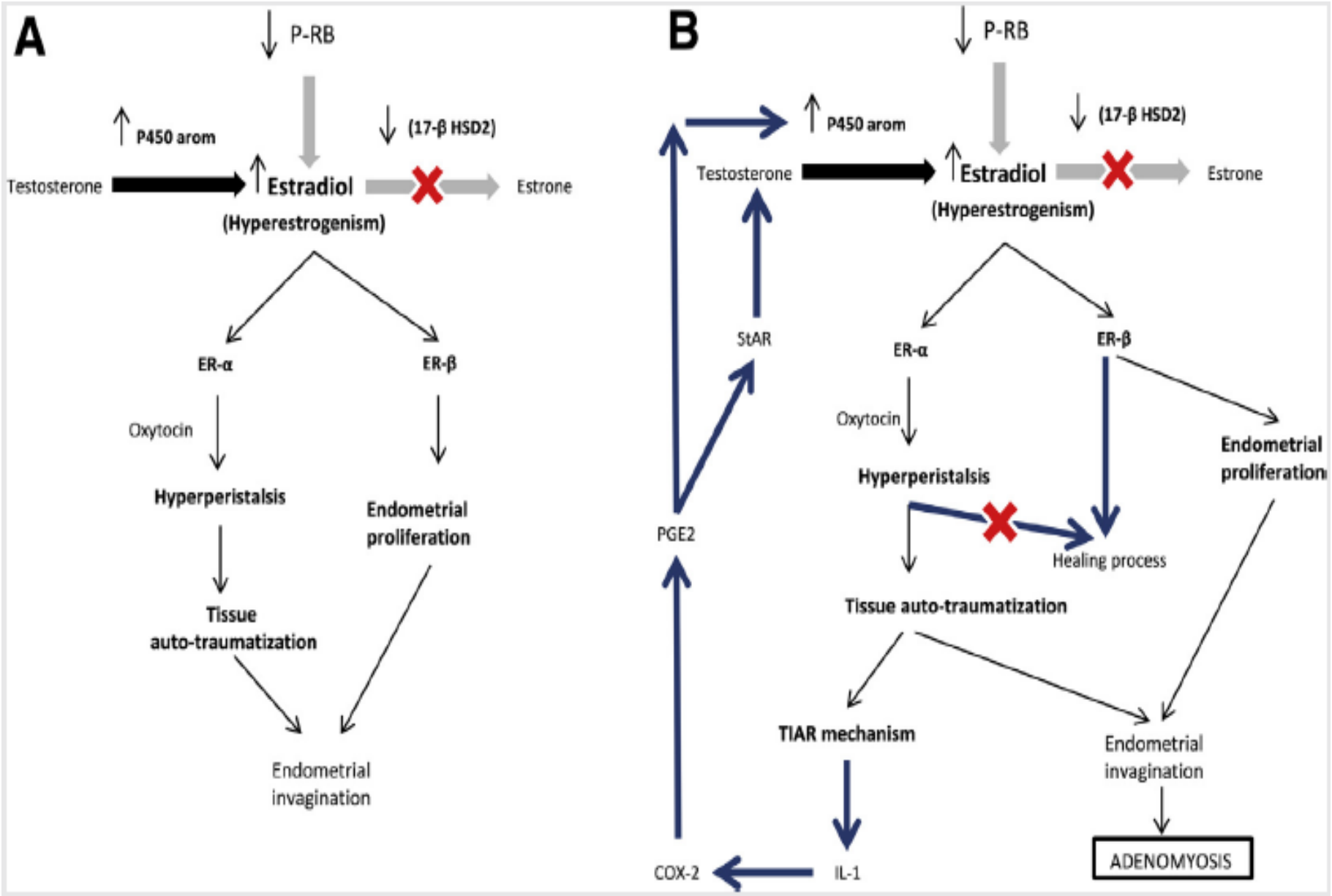


levels of antismooth muscle antibody–positive and collagen I–positive myofibroblasts are significantly higher in the JZ (evidence of tissue microtrauma)

TIAR mechanism is then activated in response to tissue autotraumatization


local
production of interleukin-
١ and induces activation
of COX-٢, causing
production of
prostaglandin E٢

Increases invagination of the endometrial basal layer into the myometrium



Invagination of the endometrial basalis: hyperestrogenism, hyperperistalsis, and TIAR mechanism activation. (A) A hyperestrogenic condition in the eutopic uterus may lead to increased proliferation in the endometrial basalis and tissue microtrauma in the vicinity of the JZ, thus allowing endometrial intramyometrial invagination. (B) As a consequence of tissue microtrauma, the TIAR mechanism is activated (blue arrows), generating a mechanism of positive feedback whereby estrogen production promotes uterine peristalsis and further autotraumatization, progressively worsening the microtrauma and endometrial invagination and eventually leading to adenomyosis establishment.

De novo development from metaplasia of displaced embryonic pluripotent mullerian remnants or differentiation of adult stem cells?

metaplastic changes of intramyometrial embryonic pluripotent Mullerian remnants in the adult uterine
wall can possibly lead to establishment of de novo ectopic
endometrial tissue within the myometrial wall, creating adenomyosis

DIE nodules were also suggested to be a possible consequence of Mullerian rest differentiation, at least in some cases, or the result of an adenomyotic tumoral process originating from the cervix,

process may explain how ectopic endometrial cells can penetrate the uterine wall and form a uterine adenomyotic nodule, or the posterior part of the cervix and form a cervical adenomyotic nodule that may extend posteriorly in the direction of the exterior wall of the rectum.


This is supported by case reports of confirmed adenomyosis in the rudimentary muscular uterine wall of patients with Rokitansky-Kuster-Hauser syndrome (absence of functional endometrium)

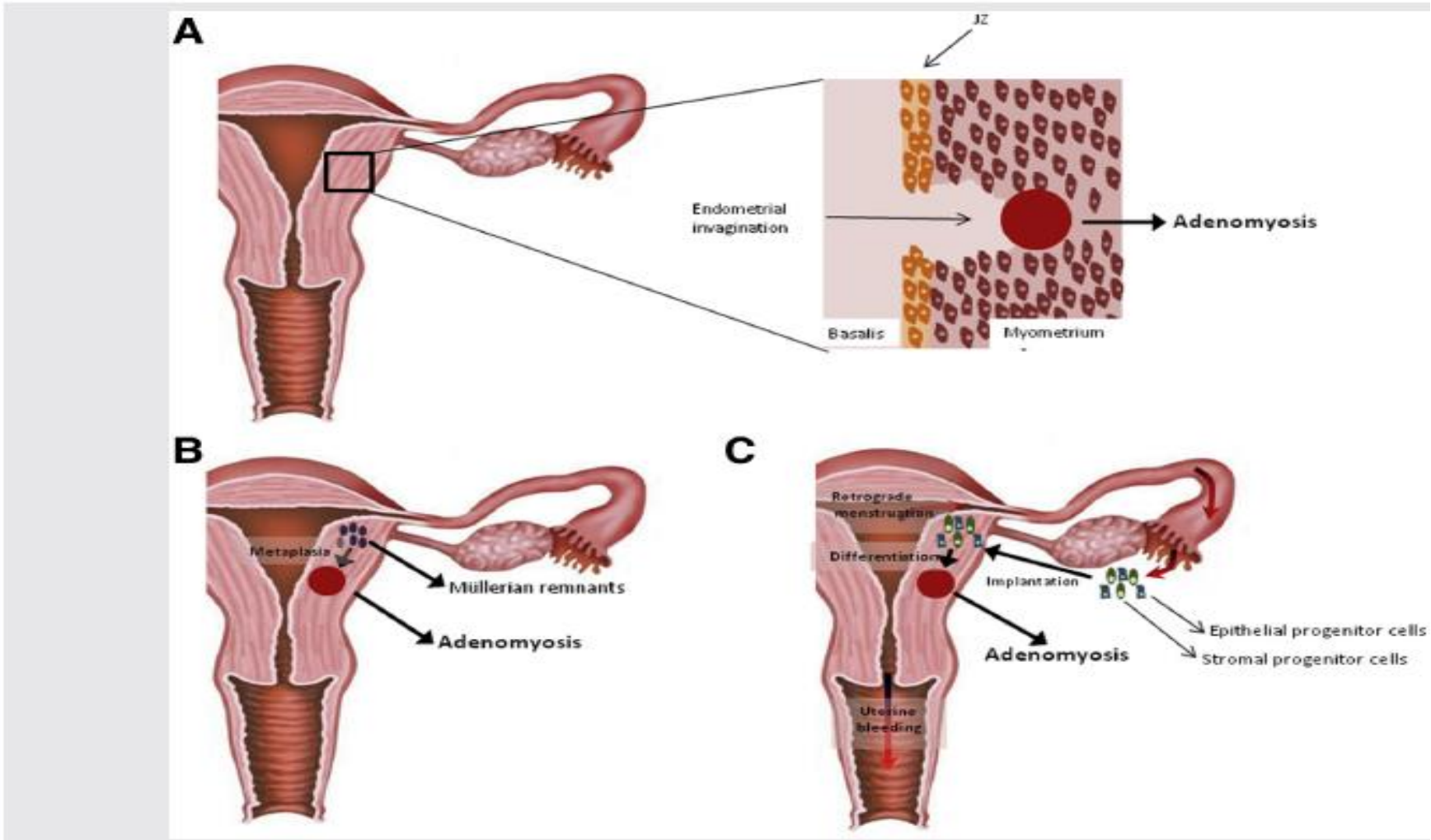
Adult progenitor stem cells may be deposited in the uterus after retrograde menstruation and differentiate into endometrial glands and stroma. These may then develop into de novo intramyometrial endometrial implants causing focal uterine adenomyosis

tissue microtrauma to the JZ and endometrial basalis may lead to abnormal alteration of the stem cell niche, allowing their differentiating progeny to move toward the myometrium rather than the endometrial functionalis, possibly resulting in adenomyosis

Vannuccini et al.
and Gargett et al

More recently, after electron microscopy examination, Ibrahim et al. described another stem cell–like population n the endometrial-myometrial interface of the fundocornual Raphe . These stem cells are located eccentrically in the epithelial glands of the basal endometrium and due to the electron-lucent appearance of their cytoplasm were called (pale cells)

pale cells may be translocated
through the basal membrane of adenomyotic glands, acquire
motile properties, and migrate toward the stromal compartment
and subsequently to the myometrium, where they can
develop into de novo adenomyotic lesions



Theories on the origin of adenomyosis. (A) Invagination of the endometrial basalis into the myometrium, after TIAR mechanism activation. (B, C) De novo formation of lesions: (B) after metaplasia of displaced embryonic pluripotent remnants or (C) from differentiation of endometrial and stromal stem cells deposited in the myometrium after retrograde menstruation

RISK FACTORS

Clinical History of Patients

- Early menarche,
- short menstrual cycles,
- increased body mass index
- history of depression
- surgical tissue damage to the endometrialmyometrial interface
- Smoking(Parazzini et al. reported lower rates of adenomyosis in smokers compared with women who had never smoked , but other studies showed either higher rates of smoking in adenomyosis patients or no association between these two factors
- estrogen exposure(controversial)
- tamoxifen to treat breast cancer

Genetic Factors

- Increased prevalence of this uterine disorder was observed in **patients carrying the null genetic variant for the detoxification enzyme glutathione S-transferase m ١ (GSTM ١) and exhibiting increased levels of urinary mono-ethylhexyl phthalate**, This indicates a possible joint effect of these estrogenic chemicals and gene deletions, giving rise to adenomyosis

Epigenetic Factors

- Increased expression of Deoxyribonucleic acid methyltransferases (DNMTs) DNMT١ and DNMT٣B was documented in ectopic endometrium from patients with adenomyosis compared with controls

CONCLUSION

- Adenomyosis is a commonly diagnosed estrogen-dependent gynecological disorder that causes pelvic pain, abnormal uterine bleeding, and infertility
- Two main theories have been proposed to explain the origin of adenomyosis. The most common suggests involvement of the **tissue injury and repair mechanism** and claims that adenomyosis results from invagination of the endometrial basalis into the myometrium. An alternative theory maintains that adenomyotic lesions result from **metaplasia of displaced embryonic pluripotent Mullerian remnants or differentiation of adult stem cells**
- Previous investigations performed in human adenomyotic lesions and corroborated by studies in mice and baboons supported the involvement of the **epithelial-mesenchymal transition process** in the early stages of progression and spread of adenomyosis and indicated **that collective cell migration** may be implicated in the later events of invasion.


thank you