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An Update on the Various Theories of the Origin of Uterine Adenomyosis –A Systematic Review

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Abstract

Adenomyosis is a frequently diagnosed estrogen based gynaecological disorder, whose pathology as well as etiology is not clear. For the origination of Adenomyotic lesions as well as modes implicated in the evolution as well as propagation of the disease, till now two basic theories had been posited like implication of tissue injury as well as repair mechanisms and promote that adenomyosis occurs via invagination of endometrium basalis in the myometrium. Another theory which says that Adenomyotic lesions occurs secondary to metaplasia of displaced embryonic pluripotent mullerian remnants or differentiation of adult stem cells. But as far as Guo's theory, both theories have apparent limitations, i.e., difficulty in falsification, explaining existing data, and making useful predictions. Based on the current understanding of wound healing, a new hypothesis, called endometrial-myometrial interface disruption (EMID), is proposed to account for adenomyosis resulting from iatrogenic trauma to EMI. The EMID hypothesis not only highlights the more salient feature, i.e., hypoxia, at the wounding site, but also incorporates epithelial mesenchymal transition, recruitment of bone-marrow-derived stem cells, and enhanced survival and dissemination of endometrial cells dispersed and displaced due to iatrogenic procedures. More importantly, the EMID hypothesis predicts that the risk of adenomyosis can be reduced if certain perioperative interventions are performed. Consequently, from a pathogenic standpoint, adenomyosis is not simply endometriosis of the uterus, and, as such, may call for interventional procedures that are somewhat different from those for endometriosis to achieve the best results.

Keywords: *TIAR; Adenomyosis; mullerian remnants; adult stem cells; EMID; EMI trauma; collective cell migration.*

Introduction

Adenomyosis is a usually found to be a benign uterine disease, afflicting 19. 5% of women of reproductive age [1]. Histopathological examination (HPE) shows presence of ectopic endometrial tissue (endometrial glands as well as/or stroma) in the myometrium, surrounded by hyperplastic as well as hypertrophic smooth muscle as well [2]. Various distribution forms are taken up by the ectopic endometrial implants in the myometrium which gives 2 major types of the disease i) focal as well as ii) diffuse. Adenomyosis is labeled focal when a circumscribed nodular form is found but diffuse if a variety of groups of endometrial glands as well as stroma are distributed throughout the myometrium [3]. Conversely in some rare cases Adenomyosis might also be seen as a huge cyst (cystic adenoma)[3,4].

Clinical features are pelvic pain as well as abnormal uterine bleeding (AUB) as well as infertility [5, 6]. but symptoms are not specific and an overlap might exist with different gynaecological diseases like endometriosis as well as a leiomyoma hence interfering with preoperative diagnosis [7,8]. A big advance in diagnosis has come via imaging techniques

like transvaginal sonography (TVS) as well as magnetic resonance imaging (MRI) which have caused main innovation in forming newer conservative therapies to get formed for treatment of Adenomyosis [9-12]. Nevertheless, the gold standard for the diagnosis of Adenomyosis still remains histological examination following surgery –details by Gordts [8] as well as Bazot [12].

Both endometriosis as well as Adenomyosis are very closely related disease [4, 13]. The rate of coexistence differs as per endometriotic phenotype that is involved, like shown recently by Chapron et al as well as Leyendecker [4,5,13]. They further have a lot of common features, symptomatology, as well as molecular changes [14-16]. Still lot of variations is there in their etiopathogenesis as well as pathogenic mediators[17].

Inspite of prevalence as well as severe symptoms not much is known regarding the etiology as well as pathogenesis of Adenomyosis.

Methods

We conducted a pubmed review of different theories suggested regarding the etiopathogenesis of Adenomyosis using the MeSH terms Adenomyosis; endometriosis; commonality of etiopathogenesis; uterine stem cells; invasion; estrogen levels; progesterone alterations; metaplasia from 1990 till date in may 2020.

Results

We found a total of 2742 articles out of which we selected 84 articles for this review.

Posit on Adenomyosis Origin

Despite etiology as well as pathogenesis not being clear 2 basic theories have been posited in the literature namely i) invagination of the endometrial basalis due to activation of the tissue injury as well as repair (TIAR) mechanism as well as metaplasia of displaced embryonic pluripotent mullerian remnants or differentiation of adult stem cells.

Invagination of the Endometrial Basalis

Steroid hormones have a main part in the etiology of adenomyosis. Actually supraphysiological estrogen synthesis (hyperestrogenism) secondary to local paracrine action in eutopic as well as ectopic endometrium of patients presenting with adenomyosis might be the initial status, that aid in the development of the disease. This concept gets corroborated by the escalated amounts of E2, usually observed in the menstrual blood of women with adenomyosis as compared to peripheral blood amounts [18].

Gene polymorphisms =>enhanced synthesis (aromatase cytochrome P450-1B1 [CYP1 B1]432 C/G as well as cyclooxygenase-2[COX-2] 1195 G/A) as well as decreased metabolism (catechol-O-methyl transferase [COMT] 158 G/A) of estrogens are correlated with a > risk of adenomyosis formation [19, 20]. Due to this hyperestrogenism is pointed to occur due to escalated local aromatization as well as decreased local estrogen metabolism in the eutopic as well as ectopic endometrium of patients presenting with Adenomyosis. Actually Aromatase cytochrome P450, which is a heme –containing enzyme that catalyzes the reactions involved in steroidogenesis, is not present within the endometrium of disease –free uteri as shown by Kitawasi et al. However it is present in the eutopic endometrium of patients presenting with adenomyosis, that facilitates estrogens biosynthesis with greater bioavailability because of local aromatization of circulating androgens (T) into E2 [21]. Decreased E2 conversion to less potent estrone was also seen in eutopic as well as ectopic endometrium of patients presenting with Adenomyosis, due to decreased expression of 17-βhydroxy steroid dehydrogenase type2(17β HSD2) enzyme[22].

Estrogen stimulated endometrium proliferation in healthy endometrium gets counteracted by P but not in patients of Adenomyosis. In these cases, stromal cells of the endometrial functionalis as well as basalis demonstrate lower immunoreactivity for isoform B of the P receptor (PR-B)in eutopic endometrium as compared to disease free endometrium, resulting in loss of its action and ultimately a mode of P resistance [23, 24]. Thus during secretory phase of cycle, estrogen-driven proliferative actions on endometrium are not fully equipped via P, resulting in abnormal endometrium proliferation. Further in Adenomyosis, hyperestrogenism might facilitate escalated oxytocin modulated uterine activity, causing escalated mechanical strains as well as stresses which could injure cells in the junctional zone(JZ)B next to the fundocornual raphe [13,25,26]. Changed endometrium proliferation as well as hyperperistalsis –induced tissue microtrauma in the JZ secondary to

supraphysiologic estrogen synthesis might hence escalate endometrial myometrial invagination (fig1A as well as 2A)[see review 27].

Actually, as proof of tissue microtrauma, amounts of antismooth muscle antibody positive as well as collagen 1 positive myofibroblasts are significantly greater in the JZ of women with Adenomyosis as compared to those without [28].

The TIAR mode then gets activated secondary to tissue autotraumatiization [13,25,26]. This mode results in a particular physiologic process which facilitates local synthesis of interleukin 1 as well as induces activation of COX-2, leading to synthesis of prostaglandin E2, steroidogenic acute regulatory proteins (STAR) as well as P450 aromatase are ultimately activated, that aids in T synthesis as well as aromatization to E2, and cause the hyperestrogenism status of the eutopic endometrium. E2 causes its proliferation as well as healing actions via E2 receptors (ER, ERβ in this case). Nevertheless in normal healing, escalated synthesis of E2 ends, but in the uterus they stimulate oxytocin modulated hyperperistalsis via ERα, that inhibits the healing process (fig1B). Hence a positive feedback mechanism gets developed, via which chronic hyperperistalsis in the JZ facilitates repeated cycles of autotraumatiization, causing a continuous disruption of the muscular fibers in the myometrial wall. This keeps on worsening with every cycle and ultimately escalates invagination of the endometrial basal layer into the myometrium, ultimately ending in the formation of adenomyotic lesions [fig1A, 2A awa 2a). Further as the expression of matrix metallo proteinases (MMPs) -2 as well as 9 were observed to be significantly greater in the eutopic endometrium of the adenomyotic lesions, which in the endometrium of the disease free women [29], it is probable that the proteases might also be involved in the intra myometrial endometrial invagination process. Additionally, since they might present with tissue damage to the endometrial myometrial interface, caesarean delivery, escalated birth rates and prior uterine surgery were shown in a lot of retrospective studies to be risk factors for adenomyosis formation [30-32], that further reinforces the critical significance of tissue microtrauma in the formation of this disease.

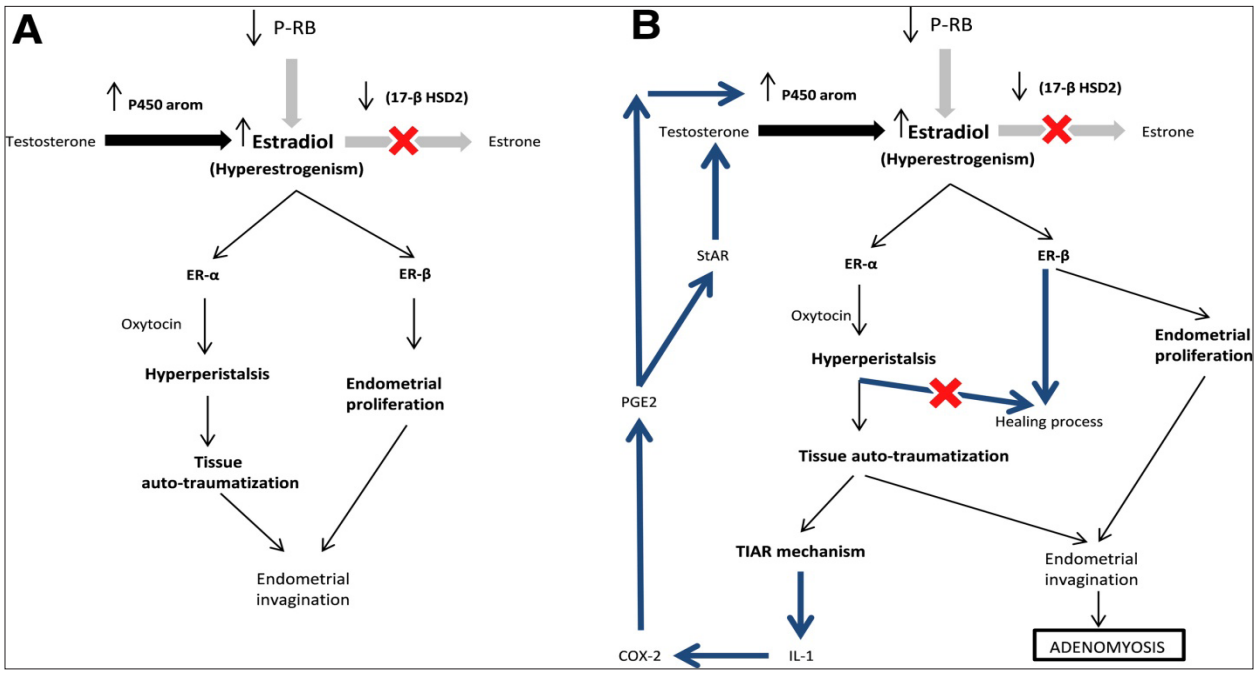

Figure1. *Courtesy ref no-27-Invagination of the endometrial basalis: hyperestrogenism, hyperperistalsis, and TIAR mechanism activation. (A) A hyperestrogenic condition in the eutopic uterus may lead to increased proliferation in the endometrial basalis and tissue microtrauma in the vicinity of the JZ, 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.*

Metaplasia of Displaced Embryonic Pluripotent Mullerian Remnants leading to Differention of Adult Stem Cells

Though a lot of human as well as experimental studies prefer the posit of endo myometrial invagination, with the current insight of adenomyotic lesions might occur de novo via metaplasia of the displaced embryonic pluripotent Mullerian Remnants or actually via differention of Adult Stem Cells [33-35] .

The Mullerian ducts represent primordial embryological structure which at the time of fetal life, form the female uterine tract (uterus, fallopian tubes, as well as the superior part of the vagina)[36]. These ducts comprise of surface epithelium as well as the underlying urogenital ridge mesenchyme with the ability to differentiate into endometrial glands and stroma [37]. It was posited that metaplastic alterations of intra myometrial Embryonic mullerian remnants in the adult uterine wall can probably result in development of denovo ectopic endometrial tissue within the myometrial wall, forming adenomyotic lesions [35] (fig2B). On the same line since their histology shows classical features of adenomyosis with smooth muscle hyperplasia as well as fibrosis, deep endometriotic nodules were also pointed to be probably secondary to mullerian rest differention, atleast in certain subjects or due to the adenomyotic tumoral lesions initiating from the cervix as pointed by Donnez et al, about 20 yrs back [38-41]. This same mode might explain how ectopic endometrial cells might penetrate the uterine wall as well as develop a form of uterine adenomyotic nodule [39, 40] which might continue posteriorly in the direction of the external wall of the rectum or the posterior part of cervix, and form a cervical adenomyotic nodule which might extend posteriorly in the direction of the external wall of rectum. Deep lesions are basically separate from peritoneal endometriosis [38,41], as well as their histology is quiet similar to that of uterine adenomyosis. The mullerian metaplasia theory gets corroborated further by case reports of confirmed adenomyosis in the rudimentary muscular uterine wall of Rokitansy –Kuster-Hauser syndrome with lack of functional endometrium [42-44].

Whereas ectopic mullerian remnants documented in both epithelial as well as stromal Adult Stem Cells having clonogenic action were found in colony forming units of endometrial as well as stromal cells derived via hysterectomy specimens [45]. It is believed that these Stem Cells remain in the endometri al basalis following menstruation [46.47]. In case of healthy endometrium, the location of Stem Cells in the endometrial basalis is a key factor for regeneration as well as replacement, but it might let uninhibited growth which might reach beyond the endometrium [48] Adult progenitor Stem Cells might get deposited in the uterus following retrograde menstruation and then differentiate into endometrial glands as well as stroma. These might then form into denovo intra myometrial implants or along with menstrual debris, develop an endometrial colony, thus forming focal uterine adenomyosis (fig2C). Though it is still not clear if endometrial fragments are shed via basalis during menstruation, in case of similar uterine abnormalities like endometriosis, escalated rates of basalis shedding were documented as compared to disease free women [49]. For analysis of potential part retrograde menstruation in endometrial Stem Cells implantation in the uterine wall further studies are needed for knowing if same menstrual patterns are seen in cases of adenomyosis .

On the other hand Vannucinini et al. as well as Gargett et al. posited that endometrial Stem Cells might get activated following tissue damage [33,34]. Thus, tissue microtrauma to the JZ as well as endometrial basalis might result in abnormal changes of the Stem Cell niche, letting their differentiating progeny to migrate towards the myometrium instead of endometrial functionalis probably causing adenomyosis formation [33,34](fig3).

Recently following electron microscopy evaluation, Ibrahim et al. detailed another Stem Cell-like population in the endometrial-myometrial interface of the fundocornual raphe [50]. These Stem Cells are present eccentrically in the epithelial glands of the basal endometrium as well as in view of electron-lucent look of their cytoplasm they were labeled pale cells [50]. In the endometrial-myometrial interface of adenomyotic women, same Stem Cells were significantly < attached to their surrounding epithelial cells (absence of desmosomal junctions) and displayed > pseudopods, as compared to what was seen in disease –free women. Thus it was pointed that adenomyosis, pale cells might get translocated via the basal membrane of the adenomyotic glands, develop motile properties and move toward the stromal compartment and then in the myometrium, where they can form de novo adenomyotic lesions [50]. This migration might get escalated by the enhanced expression of matrix

metalloproteinase(MMP)2 as well as 9 in the stromal cells in the eutopic endometrium of patients with in vivo adenomyosis [29,51].

Thus even if there is robust proof to corroborate the invagination theory, the de novo formation of adenomyotic lesions is further a probability which can't be given up. Greater researchers are required for establishing a part of mullerian remnants as well as endometrial Stem Cells in the starting of adenomyosis[52].

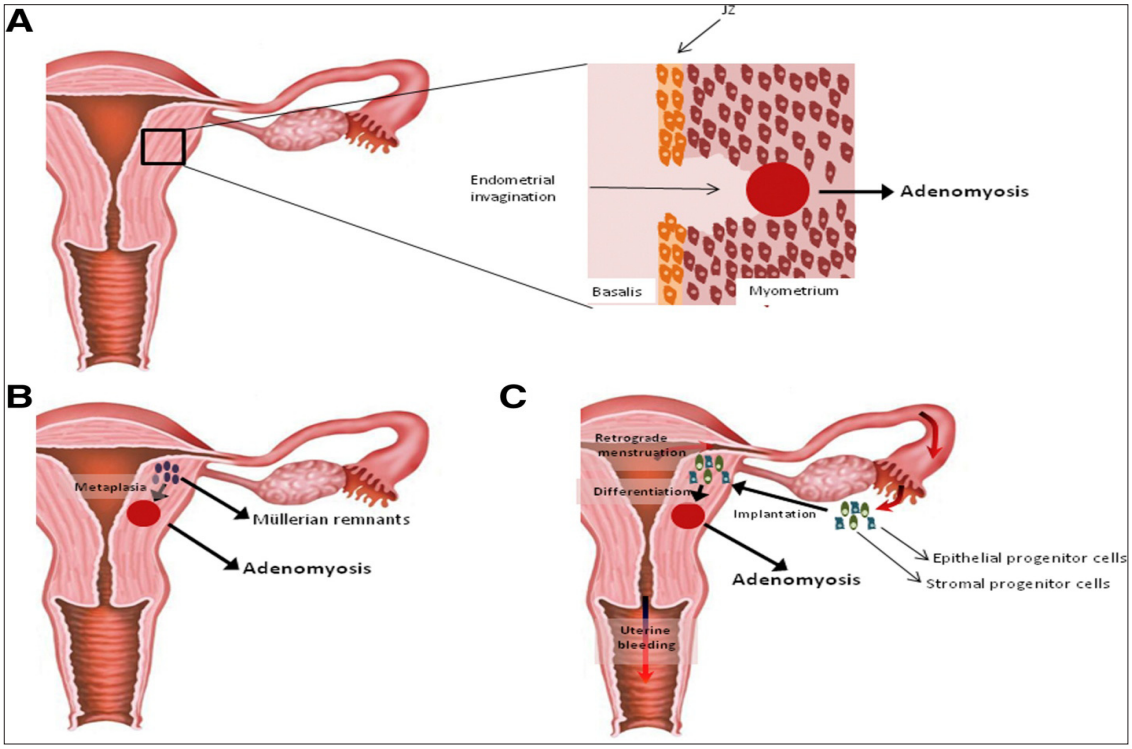

Figure2. *Courtesy ref no-27-Theories on the origin of adenomyosis. (A) Invagination of the endometrial basalis into the myometrium, after TIAR mechanism activation. (B, C) De novo formation of lesions: (B) after metaplasia of displaced embryonic pluripotent remnants or (C) from differentiation of endometrial and stromal stem cells deposited in the myometrium after retrograde menstruation.*

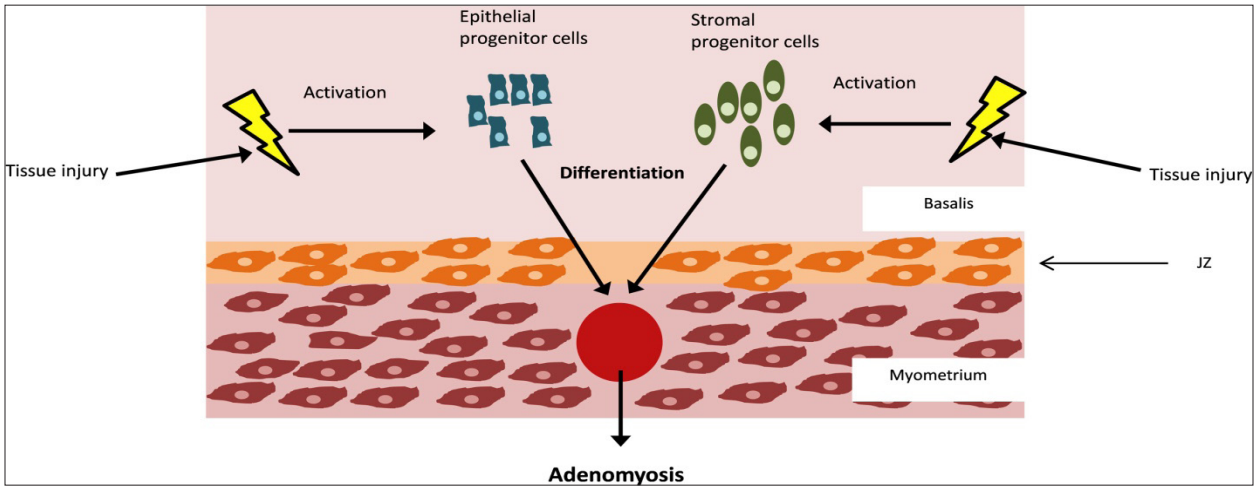

Figure3. *Courtesy ref no-27-De novo formation of adenomyotic lesions from endometrial and stromal stem cells after tissue injury. Tissue microtrauma to the JZ and endometrial basalis may lead to abnormal alteration of the stem cell niche, allowing their differentiating progeny to move toward the myometrium rather than the endometrial functionalis, possibly resulting in adenomyosis establishment.*

Pathogenic Development

Once adenomyosis gets set in, migration as well as invasion are thought to be critical factors in the progress as well as spread of lesions. EMT represents a biological function that is implicated in embryological formation as well as tissue repair as well as cancer cell migration, where stationary polarized epithelial cells lose their cell-cell adhesions as well as convert it to markedly motile mesenchymal cells, increasing their migratory as well as invasive abilities [53]. Thus functional loss of expression of the cell –cell adhesion marker E-cadherin in epithelial cells as well as simultaneous escalated expression of the mesenchymal markers N-cadherin expression as well as vimentin were found as a hall mark of Epithelial-mesenchymal transition (EMT)[54]. In case of adenomyotic lesions reduced E-cadherin expression as well as escalated expression of vimentin as well as N- cadherin were found in the epithelial cells of adenomyotic lesions as compared to normal endometrium (controls) [55], pointing that a process which corroborates and facilitates invasion as well as propagation of adenomyotic lesions might actually get dictated via EMT.

The mode that triggers EMT in adenomyosis has not been yet demonstrated. Nevertheless, in consistency with the theory of invagination as well as hyperestrogenic status of adenomyotic lesions, Chen et al. gave proof of the estrogen dependency of EMT activation in this uterine condition [55], with estrogens, ER-positive Ishikawa endometrial epithelial cells expressed great amounts of Slug, a transcription factor which regulates EMT via repression of E-cadherin [56], along with the mesenchymal muscle markers N- cadherin expression as well as vimentin than did controls [55]. These authors further demonstrated that following treatment with raloxifene, a selective estrogen receptor modulator which blocks estrogen stimulated signaling [57], the mesenchymal phenotype gets reverted, pointing that raloxifene might be an efficacious treatment to prevent EMT –induced propagation of adenomyotic lesions .

On the other hand, platelet collection as well as activation were also documented to be a probable etiology of EMT –induction in adenomyosis. Possibly in view of activation of the TIAR mode, platelets were observed to be markedly aggregated in the pericellular spaces of vimentin positive stromal cells of adenomyotic lesions [58]. Shen et al. studying adenomyosis in mice found escalated platelet aggregation as well as significantly escalated immunostaining of transforming growth factor beta (TGFβ), p-Smad 3 as well as vimentin in the ectopic endometrium of mice with adenomyosis as the disease propagated, whereas immunoreactivity for E-cadherin kept on reducing at a steady pace [59]. Subsequent studies conducted in mice showed that antiplatelet therapy actually has a potential for treatment angle [60]. Actually Liu et al. demonstrated platelet aggregation to be associated with the initiation of EMT via the activation of TGFβ1/ Smad 3 signaling pathway in human adenomyosis [58].

Conversely, in a baboon model, that got formed more recently [15], lesions accumulated 1yr following adenomyosis induction demonstrated no significant variations in the amounts of the epithelial cell-cell adhesion markers, E-cadherin as well as β-catenin among the maximum aggressive as well as the least aggressive adenomyotic glands [61]. As per Friedl et al. sustainance of cell –cell attachment is the major property of collective cell migration, a process that involves massively coordinated migration of groups of cells involved in physiological(wound healing) as well as pathological (cancer) process[62], the reason Donnez et al. posited the role of this phenomenon in the invasiveness of this disease[16,61]. Nevertheless 6mths following adenomyosis stimulation, invasive lesions showed <levels of E-cadherin as well as β-catenin as compared to noninvasive lesions [16]. These outcomes associate with the decrease, E-cadherin seen by Shen et al. following 60days in adenomyosis stimulated mouse model[59], pointing that EMT might be responsible for early disease propagation, whereas collective cell migration, is the predominant phenomena in later invasive processes in adenomyosis.

Without the mode of invasion, the cell migration event always needs breakdown as well as reconstruction of the extracellular matrix (ECM). Chen et al. very recently

demonstrated an overexpression of the nuclear transcription factor Nrf2 (erythroid –E2 –related factor 2) in the glandular epithelium of adenomyotic lesions as compared to disease free women [63]. They showed that Nrf2 overexpression has a direct association with an escalated expression of MMP9 that has a significant part in ECM degradation [63]. Parallel with this proposal, expression of MMPs-2 as well as 9, is markedly >in adenomyotic lesions as compared to normal endometrium of healthy women [29]. Further a >risk of adenomyosis was documented in women carrying MMP-1-16071 G/2G as well as MMP-21306 C/T Polymorphisms in their promoter area [64,65]. These observations might corroborate that overexpression of the nuclear transcription factor Nrf2 might trigger intramyometrial migration of endometrial implants, via the control of MMP9 as well as another MMP, hence implicates Nrf2 as well as a MMP in the pathogenic evolution of adenomyosis.

From the above details, it is understood that for facilitating their invasiveness across the myometrium, adenomyotic cells acquire migration characteristics like absence of cell-cell attachment or the ability of degrading the ECM. Moreover, the presence of intravascular adenomyotic tissue, was documented in the myometrium of adenomyotic patients, hence it is believed that in certain cases, the vascular network might also aid in the local migration as well as spread of these lesions across the uterine wall[66].

Risk Factors

Clinical History of Patients

Risk Factors relate to adenomyosis are early menarche, short menstrual cycles, escalated body mass index(BMI), as well as history of depression[31]. As described earlier, surgical tissue damage to the endometrial –myometrial interface is a Risk Factors for adenomyosis [30-32].

It is not clear if smoking is a risk factor for adenomyosis. Lower rates of adenomyosis was documented by Parazzini et al. [30] as compared to women who had never smoked, but other studies demonstrated either >rates of smoking in adenomyotic patients [67] or no correlation among these 2 factors[68].

Proof regarding correlation among adenomyosis as well as estrogen exposure is also controversial. Actually whereas Parazzini et al. [30] could not find any correlation between the risk of adenomyosis as well as utilization of oral contraceptives (OC's) . This association still needs future evaluation further, since OC's are a commonly utilized therapy for dysmenorrhea as well as heavy menstrual bleeding, that are common symptoms of patients with adenomyosis[31].

A >prevalence of adenomyosis has been published regarding women who were given tamoxifen for the therapy of breast cancer [69-71]. Tamoxifen is a nonsteroidal antiestrogen commonly utilized for treatment in postmenopausal breast carcinoma subjects. Despite blocking ER's in breast tissue, in other tissues like endometrium, it might be having an estrogenic action as well as facilitate proliferation as well as adenomyosis formation or reactivation of preexisting adenomyotic lesions.

Genetic Predisposition

Gene deletions might also enhance the susceptibility of adenomyosis. Earlier it had been documented that exposure to endocrine disruptive chemicals, like phthalates, is correlated with a >chance of adenomyosis[72]. Actually escalated prevalence of this uterine problem was seen in patients who carried null genetic variant for the detoxification enzyme glutathione S transferased μ 1(GSTM1) as well as showing escalated levels of urinary mono-ethyl hexyl phthalate [73,74]. This suggests a probable additive actions of these estrogenic chemical as well as gene deletions, giving rise to adenomyosis formation.

Epigenetic Changes

Epigenetic Changes have been found in adenomyosis. deoxyribonucleic acid (DNA) methyl transferases (DNMTs) represent a family of enzymes which catalyze the transfer of a methyl group to DNA, Causing a >compact chromatin and thus gene repression[75]. Escalated expression of DNMT1 as well as DNMT3B was reported as compared to controls [76]. Parallel to

these observations, hypermethylation of the promoter region of PRB was found in stromal cells of adenomyotic nodules, resulting in silencing of, that agreed with the previous mode of P resistance [24]. Further aberrant expression of histone deacetylases (HDACs) was also observed in women having adenomyosis. Actually, immunoreactivity of HDAC1 as well as HDAC 3 was increased in ectopic as well as eutopic endometrium of adenomyotic lesions as compared to controls [77]. This points the role of histone modifications in the etiopathogenesis of adenomyosis. Hence therapy with valproic acid, that is an HDAC inhibitor, caused amelioration of dysmenorrhea as well as hyperalgesia as well as retardation of myometrial infiltration in patients presenting with adenomyosis[24, 78-80].

Together these observations seems to point that adenomyosis just like endometriosis might be an Epigenetic disease [81, 82].

Further Kobayashi et al. focusing on etiopathogenesis of Adenomyosis is a common gynecologic disorder defined by the presence of endometrial glands and stroma within the uterine myometrium. This review focusses on: (1) current understanding of cellular and molecular mechanisms of adenomyosis-related fibrogenesis, (2) transforming growth factor beta (TGF-β)-dependent or TGF-β-independent mediators of fibrogenesis, and (3) the origin of fibrogenic myofibroblasts. They collected a literature search from PubMed and EMBASE database up to December 2018. First, causative factors of adenomyosis were classified into exogenous traumatic damage (surgical interventions, including curettage, normal delivery, or cesarean section) and endogenous traumatic damage (mechanical strain or myometrial hyperperistalsis). The mechanical forces and injury (microdehiscences) are fundamental regulators of cell behavior and central to our understanding of disease pathogenesis. Adenomyosis is characterized by abnormal response to injury and activation of myofibroblasts in the myometrium through altered barrier function of the endometrial-myometrial junctional zone (EMJZ). Second, they summarize recent advances on the molecular mechanism of fibrosis. Two distinct populations of myofibroblasts, highly myogenic cells, and nonmyogenic cells arise possibly through the TGF-β-dependent and TGF-β-independent processes. TGF-β-independent mechanisms are still intriguing and far from clear. Third, the importance and implications of resident fibroblasts, bone-marrow stem cells-derived fibrocytes, and epithelial-mesenchymal transition-derived myofibroblasts in fibrosis remain uncertain. Finally, originally adenomyosis was believed to be the single entity, but this disorder is composed of multiple heterogeneous subtypes. Key mediators of fibrogenesis may vary widely and largely depend on adenomyosis subtype. In conclusion, both cyclic mechanical strain and EMJZ weakness (microdehiscences) may be a prerequisite for adenomyosis fibrogenesis through the mechanotransduction process. Since there are significant molecular variations among affected individuals, the approach to identify key mediators of fibrosis remains challenging [83]. Further Guo SW reveiewed beyond TIAR aswell as invaginatiom In addition, two prevailing theories, i.e., invagination—based on tissue injury and repair (TIAR) hypothesis—and metaplasia, on adenomyosis pathogenesis, are briefly overviewed and then critically scrutinized. Both theories have apparent limitations, i.e., difficulty in falsification, explaining existing data, and making useful predictions. Based on the current understanding of wound healing, a new hypothesis, called endometrial-myometrial interface disruption (EMID), is proposed to account for adenomyosis resulting from iatrogenic trauma to EMI. The EMID hypothesis not only highlights the more salient feature, i.e., hypoxia, at the wounding site, but also incorporates epithelial mesenchymal transition, recruitment of bone-marrow-derived stem cells, and enhanced survival and dissemination of endometrial cells dispersed and displaced due to iatrogenic procedures. More importantly, the EMID hypothesis predicts that the risk of adenomyosis can be reduced if certain perioperative interventions are performed. Consequently, from a pathogenic standpoint, adenomyosis is not simply endometriosis of the uterus, and, as such, may call for interventional procedures that are somewhat different from those for endometriosis to achieve the best results [fig4-6].

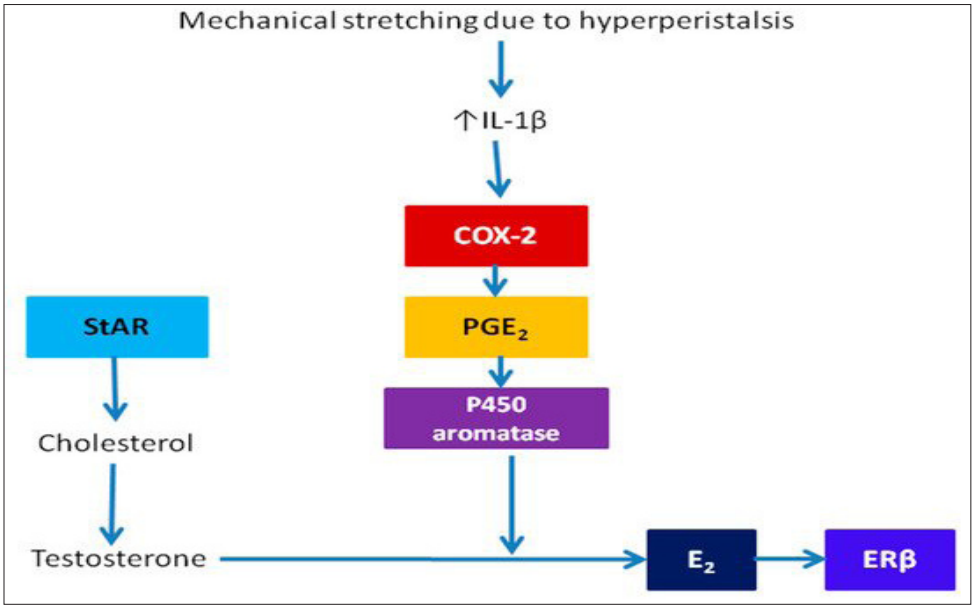

Figure4. *Courtesy ref no -84. The key molecular signaling events initiated by the tissue injury and repair (TIAR) that leads to the increased local production of estradiol, as proposed by Leyendecker et al. [25,26]. Gene/protein names: COX-2: cyclooxygenase-2; E 2 : 17β-estradial; ERβ: estrogen receptor β; IL-1β: interleukin-1β; P450 aromatase: aromatase; PGE 2 : prostaglandin E2; StAR: steroidogenic acute regulatory protein.*

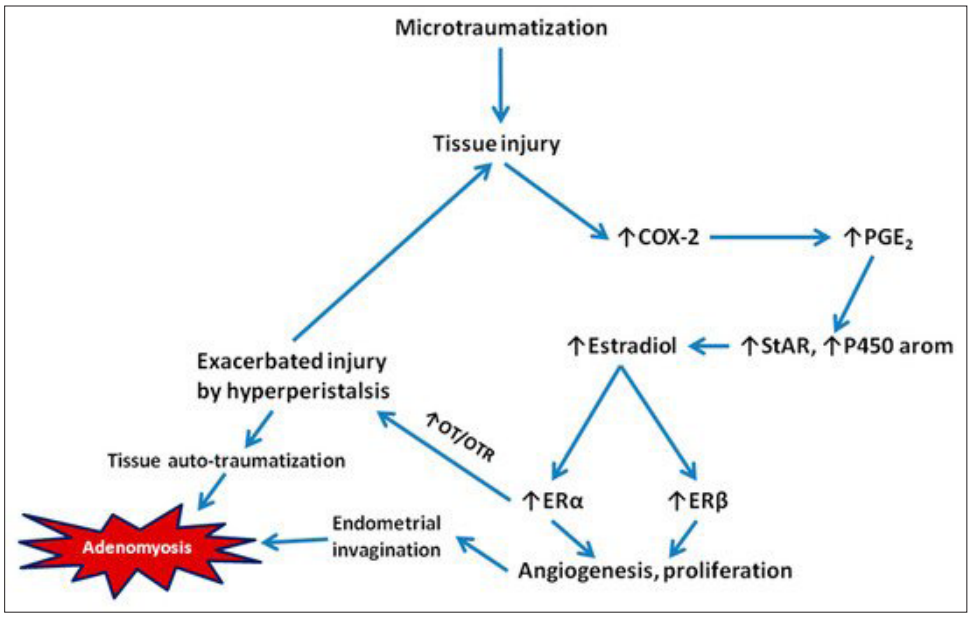

Figure5. *Courtesy ref no-84-Leyendecker's model of tissue injury and repair (TIAR) that initiates the genesis of adenomyotic lesions [25,26]. Briefly, microtraumatization in the endometrial–myometrial interface causes tissue injury, which subsequently induces upregulation of COX-2 and increased production of PGE 2 , which, in turn, induces the expression of genes critical to estrogen production such as StAR and aromatase, resulting in increased local estrogen production. The elevated estrogen levels would activate both ERα and ERβ, leading to the induction of the OT/OTR signaling and subsequent increased uterine peristalsis and increased angiogenesis and proliferation. The increased peristalsis would further exacerbate uterine hyperperistalsis and thus TIAR, causing endometrial invagination and ultimately the formation of adenomyotic lesions. Gene/protein names: COX-2: cyclooxygenase-2; E 2 : 17β-estradial; ERα: estrogen receptor α; ERβ: estrogen receptor β; IL-1β: interleukin-1β; P450 aromatase: aromatase; OT: oxytocin; OTR: oxytocin receptor; PGE 2 : prostaglandin E2; StAR: steroidogenic acute regulatory protein.*

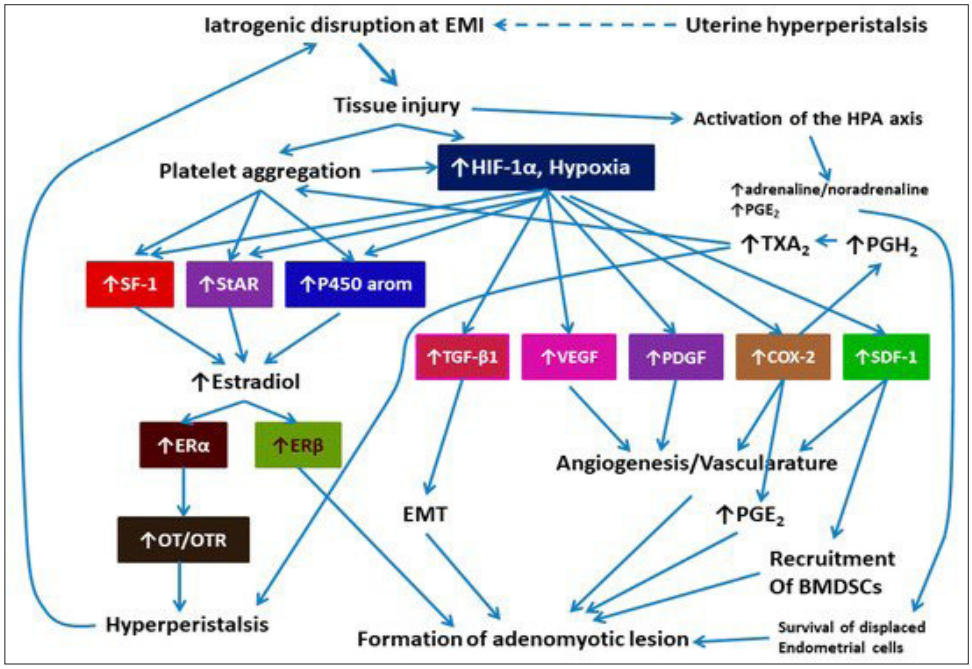

Figure6. *Courtesy ref no-84-Schematic illustration of the formation of adenomyotic lesions due to the endometrial–myometrial interface disruption (EMID). Iatrogenic procedures causes disruption at the endometrial–myometrial interface (EMI), which leads to platelet aggregation and the induction of HIF-1α, effectively causing tissue hypoxia. Uterine hyperperistalsis may also induce EMI disruption (shown in dashed arrow). As a result, genes involved in estrogen production are upregulated, resulting in increased local production of estrogen and subsequent induction of both ERα and ERβ, which, in turn, leads to the induction of the OT/OTR signaling and increased uterine peristalsis. In addition, tissue hypoxia activates TGF-β1, VEGF, PDGF, COX-2, and SDF-1 signaling pathways, leading to increased angiogenesis, vascularature, and the recruitment of BMDSCs to the wounding site. The induction of COX-2 would also increase the production of PGH 2 and TXA 2 , which also enhances uterine peristalsis. Moreover, the TGF- β1 signaling pathway induces EMT, leading to the invasion of endometrial epithelial cells to the EMI and further down to the myometrium. Tissue injury also would activate the HPA axis, leading to the release of catecholamines and PGE 2 , which collectively result in impaired cell-mediated immunity and, as such, enhances the survival of displaced and dispersed endometrial cells within the myometrium. All these events ultimately lead to the formation of adenomyotic lesions in the myometrium. Abbreviations used: BMDSC: bone marrow derived stem cells; COX-2: cyclooxygenase-2; E 2: 17β-estradial; EMI: endometrial- myometrial interface; EMT: epithelial-mesenchymal transition; ERα: estrogen receptor α; ERβ: estrogen receptor β; HIF-1α: hypoxia-inducible factor 1α; HPA: hypothalamic-pituitary-adrenal; P450 aromatase: aromatase; PDGF: platelet-derived growth factor; OT: oxytocin; OTR: oxytocin receptor; PGE 2: prostaglandin E2; PGH 2: prostaglandin H2; SDF-1: stromal cell-derived factor 1; SF-1: steroidogenic factor-1; StAR: steroidogenic acute regulatory protein; TGF-β1: transforming growth factor β1; TXA 2 : thromboxane A2; VEGF: vascular endothelial growth factor.*

Conclusions

Adenomyosis that gets diagnosed frequently is an estrogen dependent gynaecological problem which presents with pelvic pain, AUB, as well as infertility. There are basically 2 theories posited for the origin of adenomyosis. The commonest believed is the role of tissue injury as well as repair mode and probably claims which point adenomyosis occurs secondary to invagination of the endometrial basalis into the myometrium. Another theory says that adenomyotic lesions occur via metaplasia of displaced embryonic pluripotent mullerian remnants or differentiati on of adult stem cells. Earlier evaluation was done in human adenomyotic lesions as well as confirmed via evaluation in mice as well as baboons, that corroborated the role of EMT process in the early stages of propagation as well as spread of adenomyosis as well as suggested that collective cell migration might be involved in the later stages of invasion. Further. Based on the current understanding of wound healing, a new hypothesis, called endometrial-myometrial

interface disruption (EMID), is proposed to account for adenomyosis resulting from iatrogenic trauma to EMI. The EMID hypothesis not only highlights the more salient feature, i.e., hypoxia, at the wounding site, but also incorporates epithelial mesenchymal transition, recruitment of bone-marrow-derived stem cells, and enhanced survival and dissemination of endometrial cells dispersed and displaced due to iatrogenic procedures. More importantly, the EMID hypothesis predicts that the risk of adenomyosis can be reduced if certain perioperative interventions are performed. Consequently, from a pathogenic standpoint, adenomyosis is not simply endometriosis of the uterus, and, as such, may call for interventional procedures that are somewhat different from those for endometriosis to achieve the best results.

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