Endocrine Pathogenic Mediators and Molecular Mechanisms

Subjects: Obstetrics & Gynaecology

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Adenomyosis (ADM) is a multifaceted uterine pathology characterized by the ectopic infiltration of endometrial tissue into the myometrium, affecting approximately 20% of women in the reproductive age group seeking gynecological care. This condition manifests as a range of debilitating symptoms, including dysmenorrhea, menorrhagia, impaired fertility, and heightened susceptibility to miscarriage and obstetric complications. The essential dependence of ADM on estrogen and the impact of endocrine disruptors in its pathogenesis warrant further investigation, and present therapeutic opportunities.

Keywords: adenomyosis ; estrogen ; progesterone ; endocrine disruptors ; therapy

1. Intrinsic Hormonal Dysregulation

1.1. The Imbalance of Sex Steroid Hormones

Pronounced estrogen dependency is a unique characteristic of the disease and is central to its development. Indeed, the lesions develop in a hyperestrogenic environment, exhibit distinct patterns of ERs, and manifest signs of localized estrogenic effects, namely an estrogen-responsive uterine contractility. It has been three decades since elevated E2 levels were observed in the menstrual blood of a limited cohort of ADM patients, showing notably higher concentrations compared to patients with endometriosis [1]. Interestingly, increased E2 was limited to the lesions, while circulating levels were unaffected. Consequently, the localized estrogen synthesis in ectopic endometrial cells has been attributed to high estrone (E1) sulfatase levels, which activates circulating sulfated steroids and local activity of aromatase, an enzyme that converts androgens into estrogens [2]. In the context of ADM, sulfatases and sulfotransferases also contribute to the activation of steroids, particularly in the modulation of estrogen levels. Sulfatases, such as estrone sulfatase, play a role in local estrogen synthesis in ectopic endometrial cells by activating circulating sulfated steroids. Additionally, sulfotransferases are involved in the conjugation of sulfate groups onto steroids, affecting their bioavailability and enhancing their activity [3][4]. This explanation was further supported by a specific polymorphism of aromatase cytochrome P450 found in the eutopic endometrium of ADM [5][6]. The role of aromatase in ADM remains a topic of debate, with another group failing to identify a significant contribution of aromatase in endometriosis [7]. Most recently, however, clinical evidence has demonstrated the effectiveness of low-dose aromatase inhibitors in improving symptoms of ADM, such as menorrhagia, hemoglobin levels, and lesion size [8]. Using a recent transgenic murine model, Heinosalo et al. demonstrated that overexpression of the human estrogen biosynthetic enzyme hydroxysteroid, 17-beta-hydroxysteroid dehydrogenase type 1 (17β-HSD1), catalyzing the last step in estrogen activation, leads to the development of an ADM-like phenotype [9]. Conversely, the activity of 17β-HSD2, which deactivates E2 to E1, is downregulated in their eutopic and ectopic endometrium [10][11]. Two components are hypothesized to be responsible for the hyperestrogenic status observed in patients with ADM. An increased local aromatization process and a decreased local estrogen metabolism within both the eutopic and ectopic endometrium are thought to give rise to this occurrence.

Effects of High Estrogen Concentration

The local increase in estrogen concentration with normal peripheral E2 levels may cause hyperperistalsis of the uterus [12]. These specific steroids seem to create a paracrine effect, presumably mediated by the endometrial oxytocin (OT) signaling. This estrogen dominance is considered the "primum movens" in the chain of key events [13].

Hypersensitivity to Estrogen

The higher risk of developing ADM is associated with hypersensitivity to estrogen via specific polymorphism and relatively increased expression of ERα. A decreased expression of progesterone receptor isoform B (PR-B) is also understood to intensify the risk of developing ADM. Concerning the cognate receptors, ERα (NR3A1) and ERβ (NR3A2), membrane

ERα and β, and G protein-coupled ER (GPER) were expressed significantly more in ADM than in normal myometrium. These findings are the same as those in endometriosis. The ERα isoform plays dominant roles in uterine development and estrogen sensitivity during the early proliferative phase and differential subtype expression in later phases [14][15]. Accordingly, ERα mediates the E2-induced uterine epithelial cell proliferation of human endometrial cells [16]. Given the central role of this isoform, an in vivo study discovered specific *Pvu*II restriction fragment-length polymorphisms (PP, Pp, pp genotypes) of the ERα gene in ADM patients. The findings suggested a protective characteristic of the P allele, as well as how the local estrogenic effect is more potent with the P allele than with the p allele. Even if it is still unclear how the ERα gene polymorphisms influence its protein function, the authors suggested a possible explanation by a modulation of the ligand estrogen [17]. The ERβ isoform was described as upregulated in adenomyotic lesions and was proposed to be responsible for inflammation in ADM [18]. In regard to the GPER receptor, it enhances contractile responses to OT in the myometrium, seemingly supporting the TIAR theory in ADM [18][19].

Progesterone Resistance

Also proposed is the notion that progesterone resistance may contribute to the hormonal imbalance theory in ADM, as with endometriosis [20]. With this in mind, the proliferative effect driven by hyperestrogenism is not enough when counteracted by progesterone during the secretory phase of the cycle. As a result, hyperproliferation of the endometrium is promoted [21].

The predominance of ERβ over ERα leads to the suppression of PR-B expression and thus the development of progesterone resistance. PR-B and PR-A, two isoforms of the nuclear receptor PR, have dynamic cellular localization, influencing the effect of progesterone. PR-B can promote uterine epithelial cell proliferation but only when not repressed by PR-A. In ADM, PR-B was reportedly suppressed by DNA hypermethylation. Conversely to endometriosis, however, a recent study did not find decreased expression of progesterone membrane receptors in ADM, suggesting molecular differences between ADM and endometriosis [18].

Summary on Sex Steroid Dysregulation

In short, the highly localized concentrations of estrogen combined with altered expression of steroid receptors are central mechanisms leading to ADM (**Figure 1**). The local conversion of androgens and estrone sulfate into estradiol is catalyzed by increased activity of CYP19A1, STS (steroid sulfatase), and 17βHSD1 enzymes. Additionally, an altered expression pattern of steroid receptors (Erβ >> Erα > PRA > PRB) contributes to ERβ hyperactivation and progesterone resistance. These characteristics lead to reduced decidualization, increased proliferation of endometrial and myometrial smooth muscle cells, and endometrial angiogenesis. Together, these are key elements in the onset and progression of ADM lesions [10].

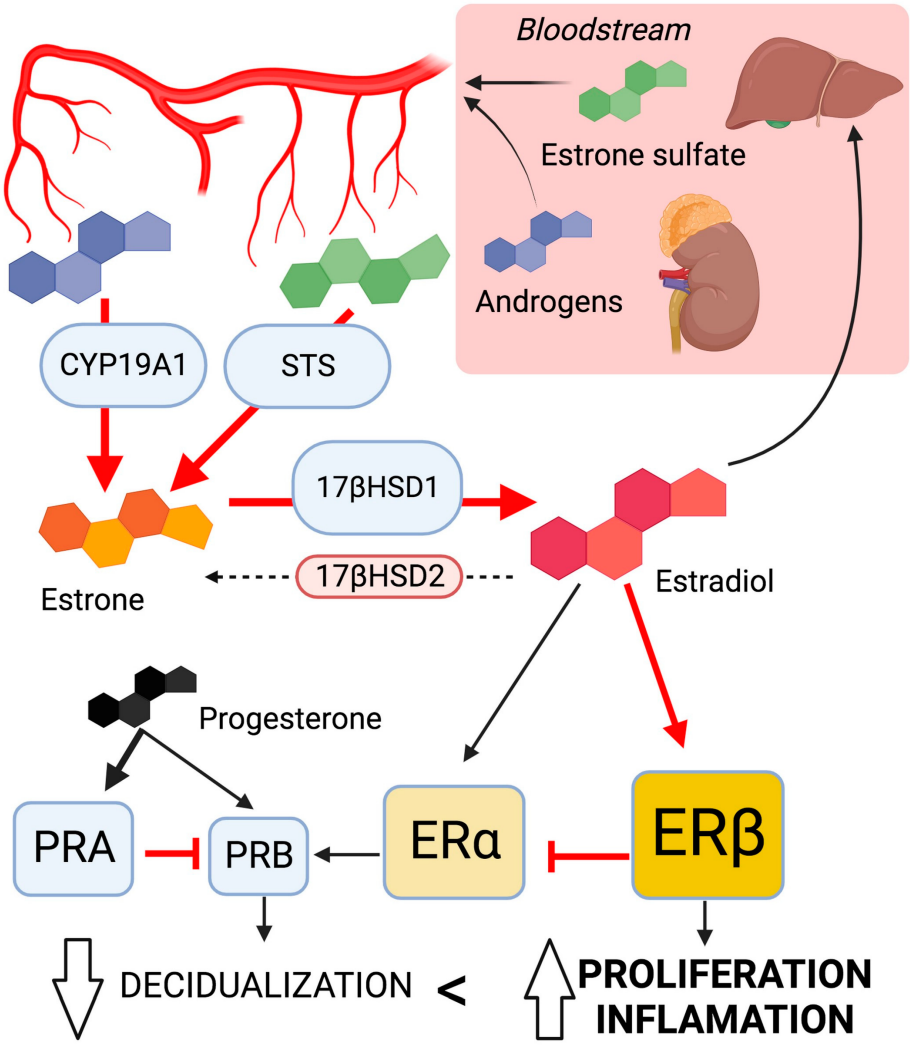

Figure 1. The dysregulation of sex steroid signaling; involvement in the development of ADM lesions leads to local hyperestrogenism. Changes in key enzyme activity promote estradiol synthesis. The altered pattern of steroid receptor expression enhances estrogen response while suppressing progesterone response. Ellipses represent enzymes; object size correlates with activity. Squares represent sex steroid receptor; object size correlates with expression levels. Arrows indicate the predominant direction in ADM lesions. Created with biorender.com.

1.2. The Pituitary Gland Influence

Prolactin

Several in vivo studies identified the role of prolactin (PRL) in ADM. In 1981, an ectopic anterior pituitary gland transplantation into the uterine lumen was sufficient in inducing ADM in mice. Circulating levels of PRL were consistently higher in pituitary isograft mice than in control mice with submaxillary gland grafts. This emphasizes the significant role of PRL in synergy with ovarian steroid hormones. Indeed, steroid supplements were necessary in pituitary grafts of ovariectomized mice to induce ADM [22]. Similar results were obtained after the administration of PRL or dopamine antagonists, inducing hyperprolactinemia. Moreover, induced ADM mice exhibited a significant upregulation of the messenger ribonucleic acid (mRNA) coding for PRL receptors [22][23]. These early findings were confirmed when observed in spontaneously occurring bovine ADM, where the levels of PRL and its receptors were found to be abnormally high during necropsies. When cells were isolated in vitro, E2 decreased the expression levels of PRL receptors in non-adenomyotic stromal cells and adenomyotic myometrial cells while increasing the secretion of PRL in adenomyotic myometrial cells [24]. In a murine model of ADM exposed to a potent suppressor of pituitary prolactin secretion, the treatment resulted in the absence of adenomyosis in all 39 experimental mice at 12 months of age, while 46.9% of 32 control mice developed the condition. These findings indicate a potential protective role of dopamine agonists within the context of ADM [24][25]. Validating this preclinical data, serum PRL is reported to be higher in patients with ADM than controls. A correlation was even suggested between the rise of PRL levels as an adverse effect of serotonin reuptake inhibiting antidepressants and the development of ADM [26]. The hyperprolactinemic state leads to the invasion of endometrial stromal cells and then glands into the myometrium. This coincides with the overall loosening and disruption of the myometrial layer and the disintegration of individual muscle cells [27]. Moreover, PRL enhances E2 actions in the uterus and stimulates ER expression in the endometrium. This initiates a vicious cycle within the ADM myometrial cells

[24]. If not a sufficient explanation for the whole process by itself, the surgical act of grafting mice may cause mechanical disruption, aiding the invasion of endometrial tissue [28]. The intravaginal administration of bromocriptine, a dopamine agonist reducing PRL level, proved significant in decreasing menstrual bleeding and pain [29].

Oxytocin

Through estrogen-mediated contractions in the inner myometrium, OT is suspected to intervene in the microtrauma of the JZ event. It provokes hyperperistalsis of the myometrium via the cognate OT receptor (OTR), resulting in the TIAR effect. OTRs are expressed both in normal endometrium and myometrium, but their expression fluctuates with the cycle phase [30]. However, high non-cyclic expression was observed in a histological biopsy from ADM patients [31]. OTR expression at the JZ is higher in the fundal region of ADM uteri compared to control during the proliferative phase. Moreover, expression of the OTR was lower in the isthmic region than in the fundus region of ADM uteri during the proliferative phase, which is the opposite of control uteri. The dysperistalsis event can be explained by the overexpression of the fundal myometrial OTR in pathological uteri. The opposite expression pattern between fundus and isthmus may even interfere with fertility and the sperm track by disturbing the direction of the JZ contractions [32]. Furthermore, relative overexpression of the OTR in the myometrial cells of ADM patients combined with high-amplitude muscle cell contractility was positively correlated with the severity of dysmenorrhea in patients with ADM. Thus, treatments known to reduce OTR expression, like deacetylase inhibitors and andrographolides, hold potential in treating ADM [33].

Insulin-like Growth Factor 1

Insulin-like growth factor 1 (IGF1) is a multifaceted factor that plays a pivotal role in regulating growth and development. In the uterus, IGF1 is essential for adequate decidualization of the endometrium and directly affects fertility. Significant hormonal crosstalk exists between estrogen and IGF1. E2 enhances IGF1 synthesis and IGF1 potentiates the effects of estrogen [34]. In the endometrium, IGF1 expression and secretion are prominent in stromal cells, while IGF1 receptors are expressed in epithelial cells. In patients with ADM, the expression of IGF1 receptors is significantly elevated, contributing to the aberrant growth of endometrial tissue within the uterine wall [35]. IGF1 may exacerbate inflammation and fibrosis. Furthermore, the interplay between IGF1 and estrogen could further promote lesion formation. These findings warrant greater research to fully elucidate the precise mechanisms by which IGF1 contributes to the development and progression of ADM.

1.3. Genetics and Epigenetics Alteration of Endocrine Signaling

Genetic variants influence enzyme activity and increase the risk of estrogen dependency in ADM. In particular, cytochrome P450 (CYP) and catechol-O-methyltransferase (COMT) gene variants are involved [36]. When comparing ADM to disease-free patients, a recent study found an increased frequency of the C allele in T/C and C/C genotypes of the CYP1A1 gene (CYP1A1 M1 polymorphism), the A allele in C/A and A/A genotypes of the CYP1A2 gene (CYP1A2*1F polymorphism), and the T allele in C/T and C/C genotypes of the CYP19 gene (Arg264Cys polymorphism). The study also found a decreased frequency of the mutant allele and heterozygous and mutant homozygous genotype of the CYP1A2 gene in ADM patients. These results suggest that ADM is triggered by the active hormones and their metabolites' higher concentration due to enzymes under these polymorphisms' influence [36].

Another presumption is that the KRAS gene mutation is part of the genetic predisposition to ADM. Among micro-dissected eutopic samples, KRAS mutations were observed in 55.6% of those with ADM, 50% of those with endometriosis, and only 29.1% of the disease-free cohort [37]. KRAS-activating mutations stimulate signaling pathways to enhance cell survival and proliferation and are associated with progesterone resistance in ADM [38]. Recent findings support genetics as a driver in the pathogenesis of ADM through alterations in gene functions, governing not only the steroid function but also the extracellular cell matrix dysregulation, angiogenesis, TIAR mechanism, and inflammatory mediators.

Evidence also reports several types of epigenetic alterations in ADM. In relation to the deoxyribonucleic acid, increased expression of deoxyribonucleic acid methyltransferases DNMT1 and DNMT3B were found in the ectopic endometrium of ADM patients [39]. These enzymes catalyze the transfer of a methyl group to DNA for gene silencing [39][40]. Therefore, they are a candidate for explaining the hypermethylated status of the PR gene observed in ADM and its progesterone resistance [41]. Histone epigenetic modification is a second potential mechanism of the disease. Aberrant expression and localization of class I histone deacetylases (HDACs) was demonstrated in the endometrium, and the immunoreactivity of HDAC1 and HDAC3 was elevated in the adenomyotic endometrium (both ectopic and eutopic) [42]. Hence, the use of valproic acid, a well-known HDAC inhibitor, has been proposed as an effective treatment in refractory disease based on murine observations [43]. In patients with ADM, alterations in epigenetic modifications were detected in RNA molecules. A decrease in RNA methyl regulators and, specifically, lower levels of N6-methyladenosine was observed in the pathological

endometrium compared to controls. This contributes to an increase in the expression of various factors, including IGF1 [44]. Finally, the expression of regulatory microRNAs was dysregulated in the eutopic endometrium of ADM patients, including namely members of the miRNA-200 family pivotal in EMT, and Let-7 involved in cell cycle control. The detailed discussion of those examples can be found in the review by Khan et al. and will not be included here [45]. Although there is continuing evidence from several studies that support the involvement of the epigenetic system in ADM, additional research is needed to conclusively pinpoint epigenetic aberrations as a mechanism of disease upgrowth.

2. Extrinsic Factors

Various environmental factors have been associated with ADM development, particularly regarding endocrine disruptors (**Figure 2**).

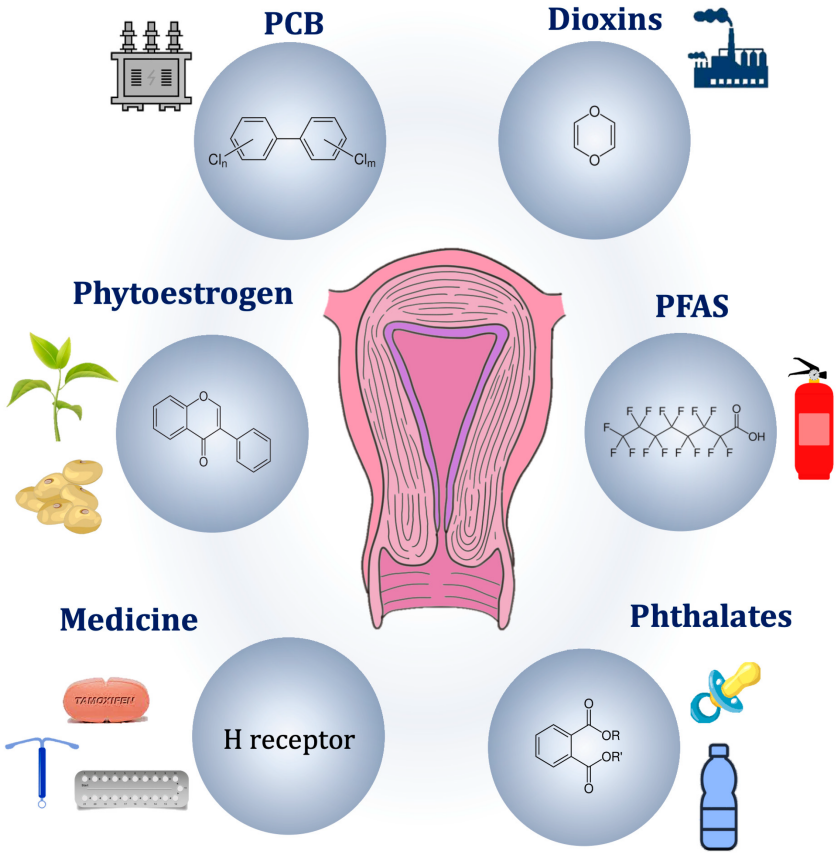

Figure 2. Potential environmental pathogenic causes of adenomyosis.

2.1. Medical Therapies

A possible correlation between the use of hormonal contraceptives and the occurrence of ADM has been considered, but a consensus has not been reached yet. Templeman et al. proposed a positive association between past hormonal contraceptive use and ADM onset, yet ambiguity persists regarding whether subjects primarily employed contraception for birth control or symptom management [46]. It is plausible that the use of the hormonal contraceptive was preferred by the patients already experiencing ADM, rather than the contraceptives being a risk factor for the development of the condition. Conversely, Parazzini et al. could not establish significant association between ADM and a history of hormonal contraceptive use [47][48]. While heightened exposure to exogenous estrogen through hormonal contraceptives may contribute to the development of lesions, such exposure could lead to a reduction in endogenous estrogen production, thereby lowering the risk of ADM [49]. Continued research is necessary to clarify the specific relationship between hormonal contraceptive use and ADM, considering the various reasons for contraceptive use among individuals.

Tamoxifen (TAM) is the prototypical selective ER modulator (SERM), a class of non-steroidal drugs exhibiting agonist and/or antagonist effects given the target tissue. TAM displays anti-estrogenic effects in breast tissue and pro-estrogenic activity in uterine tissue. Due to its demonstrated impact on endometrial tissue, the use of TAM has been identified as a risk factor for ADM [49]. Clinical findings showed that women undergoing treatment for breast cancer with involving TAM are at a higher likelihood of developing ADM than control patients (53% compared to 18%) [50]. Mice studies complemented the human data by revealing an association between TAM exposure and ADM development and progression as mice aged. Interestingly, the study uncovered significant contributions of platelets in the development of

TAM-induced lesions, affirming their involvement in the disease and indicating that TAM induces ADM through the TIAR mechanism [51][52].

Boizet-Bonhoure et al. recently demonstrated the effects of chronic exposure to environment-relevant doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen and diclofenac) combined with 17β-ethinylestradiol, in causing ADM development in mice. The research findings revealed impact in both the F1 and F2 generations, implying the occurrence of epigenetic changes [53].

2.2. Endocrine Disrupting Chemicals

Endocrine disrupting chemicals (EDCs) are exogenous compounds that interfere with the endocrine functions, potentially affecting health and promotion of disease [54]. EDCs can be divided into persistent and non-persistent organic pollutants (POPs, nonPOPs), based on their lipid solubility [55]. Both groups are lipophilic, but nonPOPs have a lower lipid solubility, resulting in a short half-life in humans. On the other hand, POPs are not readily biodegradable. Their bioaccumulation in the adipose tissue and slow release in the bloodstream account for the long-term effects [56]. Unfortunately, industrialization has made exposure to EDCs inevitable, either through packaged consumer products or contaminated foods. Since the end of 20th century, warnings have been issued against the harmful effects of EDCs, prompting the ban of polychlorinated biphenyls (PCBs), dichloro-diphenyl-trichloroethane (DDT), and diethylstilbestrol (DES) [57].

Animal studies conclusively demonstrated that EDCs are sufficient to induce ADM or endometriosis. Specifically for ADM, murine studies contributed to the understanding of the role and toxicity of EDCs [58][59][60]. The significant clinical coexistence of both conditions within a patient strongly supports a high probability of a causal relationship between EDC exposure and the initiation of endometrium-related diseases [56]. The probable association of early life exposure to EDCs with ADM offers valuable insights for therapeutic approaches and essentially its prevention [61].

Persistent Organic Pollutants

POPs are a group of synthetic chemicals resistant to environmental degradation, such as PCBs (mainly used as insulant), perfluoroalkyl substances (PFAS, notably in firefighting foams and non-stick cookware), tetrachlorodibenzo-p-dioxin (TCDD, present in Agent Orange), and dichlorodiphenyltrichloroethane (DTT, insecticide). They persist in the environment for decades, or even centuries, and can bioaccumulate in trophic networks. The hydroxylated metabolites of POPs can also have estrogenic activity.

Multiple epidemiological studies investigated the involvement of PCBs in the context of endometriosis [61]. Reflecting potential prenatal exposure, a Chinese study reported a notable correlation between a shorter anogenital distance amongst patients diagnosed with endometriosis or ADM [61]. Moreover, the sum of PCB levels was significantly higher in patients with rectovaginal ADM compared to patients with endometriosis and controls.

The ENDO study found that two types of PFAS were associated with increased incidence of endometriosis diagnosis. No association has been reported for ADM yet [62].

Association studies established a link between TCDD and endometriosis [63][64]. TCDD has the capacity to modulate signaling pathways mediated by the steroid hormones in the normal uterine physiology [65]. Bruner-Tran et al. conducted a retrospective investigation to identify mice with ADM-like lesions resulting from any type of exposure to TCDD over multiple generations [58][66]. Deep adenomyotic lesions were detected in more than half of the mice with a history of either direct (F1-F2) or indirect (F3) exposure [58]. Nonetheless, further studies are needed to assess a potential link between TCDD and ADM.

Non-Persistent Organic Pollutants

NonPOPs, such as glyphosate, phtalates, bisphenol, and pyrethroids, can degrade and break down relatively quickly in the environment, often within days to months. They are typically less likely to bioaccumulate in organisms than POPs and have lower potential for long-range transport through air and water.

Clinical studies address the potential role of gene–environment interactions in the context of ADM. Huang et al. revealed an increased risk for ADM in individuals who carry the glutathione S-transferase M1 polymorphism (GSTM1) and are exposed to high levels of phthalates compared to those unexposed [67]. Although rare cases of EDCs induce genetic mutations, most EDCs are unable to alter DNA sequences. Conversely, an association between epigenetic modifications and EDC exposure has been expressed. Some toxic agents in the environment were also proven to generate epigenetic modifications within the germline, hence causing multi- and transgenerational repercussions [68]. Despite a lack of

evidence regarding the exact bond between EDCs and epigenetics, it seems like they act with two mechanisms: gene-specific and global action [69].

Phthalates are EDCs characterized by an anti-androgenic and pro-estrogenic effect [70]. The concentration of phthalates in endometriosis patients' blood is significantly higher than in control patients [71][72]. Other studies showed an increase in urinary phthalates in patients suffering from endometriosis [67][73]. Similar results were seen in an additional study from this group that identified a modest increase in urinary phthalates in patients with either endometriosis or ADM [74]. In a case–control study, urinary levels of phthalates, particularly MEHP (the primary metabolite of DEHP), were higher and strongly associated with significantly increase in risk for ADM (OR = 10.4; 95% CI, 1.26–85.0) [67].

Bisphenols are estrogen-mimicking molecules that maintain a low concentration of PRs, eventually leading to uterine cyclicity disruption [75]. Using a murine model, Newbold et al. identified a correlation between BPA neonatal exposure and suggested a link between parental EDC exposure and the onset of endometriosis and ADM in the female offspring [76]. In 2010, another research group demonstrated that prenatal exposure to BPA in mice caused development of endometrial glands and stroma within adipose tissue neighboring the reproductive tract, accompanied by the expression of ERs and HOX-A10 [59]. However, the substantiating evidence linking BPA to ADM remains relatively scant in comparison to its association with endometriosis.

Diethylstillbestrol (DES) is a synthetic potent estrogen that was given to mitigate the risk of pregnancy loss but was prohibited in the 1970s following the disclosure of significant morbidities to females and their female offspring [77]. Further studies highlighted a link between in utero exposure to DES and the risk of endometriosis [78]. Although epidemiology studies have not identified a link between DES exposure and ADM in humans, mice studies suggested a positive correlation between DES and ADM [79][80].

2.3. Natural Endocrine Disruptors

Phytoestrogens can function as endocrine disruptors by binding to ERs and either mimicking or blocking the effects of natural estrogen. These actions can result in hormonal imbalances. They can exert ER-independent mechanisms of action, such as altering hormone-binding globulin levels. Furthermore, some phytoestrogens inhibit aromatase and other enzymes involved in the synthesis of steroid hormones. Several studies have suggested that phytoestrogens may be involved in the development or progression of uterine diseases, such as endometrial cancer [81][82].

2.4. Mode of Action of Endocrine Disruption

Most endocrine disruptors act gene-specifically by interfering with NR function, but global action is considered. NRs regulate gene-specific chromatin states by engaging histone modifiers and recruiting DNMTs and thymine DNA glycosylases (TDGs) to specified genomic loci [83]. This is supported by different studies in mice, though still not demonstrated in humans [60][84]. EDCs act globally on DNMTs by downstream regulation of messenger RNA and/or microRNA expression by defective receptors [85][86]. Moreover, studies showed a dysregulation of DNA demethylases and histone-modifying enzymes by EDC exposure [87][88].

Based on current scientific knowledge, endocrine disruptors can have an agonist or antagonist effect on hormone receptors or alter hormone receptor expression, as described with the TCDD and decreased PR expression in mice uteri [89]. EDCs, with the help of EDC co-factors, are also linked to a perturbation of both nuclear steroid receptors and cell surface membrane receptors, causing a dysregulation of downstream signal transduction [90][91]. Furthermore, they can alter the activity of hormone-responsive cells by interfering with hormonal transport [90].

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