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(REVIEW ARTICLE)

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Biochemical mechanisms linking estrogen levels to Gastroesophageal Reflux Disease (GERD)

Suaad Muhammed Abd-Alqader *

Department of Clinical Laboratory Science, College of Pharmacy, University of Basrah, Basrah, lard.

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Abstract

Gastroesophageal reflux disease (GERD)-A frequent gastro-esophageal manifestation that presents as the reflux of gastric contents into the esophagus causing symptoms such as heartburn and regurgitation; this is with and without some apparent mucosal injury. GERD is a significant burden in terms of the impaired ability to function in daily life, sleep quality, and overall quality of life, and it can develop a whole series of complications such as erosive esophagitis, Barrett's esophagus and esophageal adenocarcinoma. Notable sex-related differences in the presentation & outcome of GERD point to possible sex hormone, particularly estrogen, roles in the disease pathophysiology. Estrogen receptors are in fact present along the gastrointestinal tract including epithelial of the esophagus, lymphocyte, and smooth muscle suggesting that estrogen signaling may modulate both reflux mechanisms and the condition of tissues. The objective of this narrative review is to provide a summary of biochemical mechanisms through which the level of hormones and hormone signaling pathways affect the symptoms of GERD and associated complications. A thorough literature search was performed based on PubMed database search, focusing mainly on studies that have been published the last 10-15 years. Key search terms were GERD, estrogen, estradiol, estrogen receptors, nitric oxide, lower esophageal sphincter, hormone replacement therapy and pregnancy. Evidence from human and animal studies indicates that estrogen may have a beneficial effect on reflux episodes, because of the nitric oxide relaxation of the lower esophageal sphincter throwing out of balanced control of gastroesophageal reflux. On the other hand, estrogen seems to have protective effects in the esophageal mucosa by improving the epithelial barrier integrity by regulating tight junctions and modulating inflammatory responses. These dual and sometimes opposing actions point to the complexity of the role of estrogen in GERD pathogenesis. Further mechanistic human studies combining hormonal measures and formulations of objective reflux parameters, as well as mucosal injury, are required to elucidate the clinical importance and therapeutic implications of estrogen in the pathogenesis of GERD.

Keywords: GERD; Estradiol (E2); Estrogen Receptors (Erα/Erβ); Hormone Replacement Therapy (HRT); Barrett's Esophagus

1. Introduction

Gastroesophageal reflux disease (GERD) is commonly described as the back-up of gastric contents into the esophagus with bothersome symptoms including heartburn and regurgitation, with or without visible mucosal injury, and can develop into erosive esophagitis, Barrett's esophagus, adventitious stricture and far less commonly adenocarcinoma. Population data indicates that the prevalence of reflux symptoms vary considerably across countries and study definitions and this enhances the view that GERD is a heterogeneous condition and not a single uniform phenotype [1]. In current clinical research, modern frameworks focus on the delineation between proven GERD versus unproven GERD with use of objective evidence such as endoscopy and reflux testing given that the burden of symptoms alone is not always reflective of mucosal injury and/or risk for development [2]. Importantly, the sex and gender patterns in

* Corresponding author: Suaad Muhammed Abd-Alqader

symptom profiles and health-related quality of life have been reported in patients with gastroesophageal reflux disease (GERD), having strong evidence that there may be biological and psychosocial modifiers that may influence the presentation and the experience of the disease. Estrogen is biologically relevant in this context as estrogen and estrogen receptors are biologically active throughout the GI tissues including the epithelial [3], immune, and smooth muscle compartments, and therefore estrogen signaling could plausibly affect GI motility, inflammatory responses and the integrity of the epithelial barrier.

Building on this rationale, the aim of this narrative review is to synthesize biochemical mechanisms between estrogen levels and estrogen signaling and GERD phenotypes (symptomatic GERD, nonerosive reflux disease [4], erosive reflux disease) and GERD-related complications and use clinical context of hormonal fluctuation or exposure to clarify mechanistic inference. From a pro-reflux point of view, we know from experimental studies that estradiol can cause ex-vivo relaxation of the lower esophageal sphincter tissue, providing a plausible mechanism for the way in which estrogen might cause reflux episodes, due to decreased sphincter tone and altered neuromuscular control [5]. Parallel to this, it has been suggested that estrogen may be of possible importance to the esophageal barrier defense as part of the mucosal integrity and barrier functions causes that may hypothetically reduce the susceptibility to esophageal erosive injury despite the presence of reflux [6]. Clinically, menopausal hormone therapy has been linked to increased odds of GERD in a recent systematic review and meta-analysis, suggesting HRT to serve as a useful real world model to study the risk of symptoms associated with estrogen exposure. , and pregnancy-centered evidence-based reviews emphasize that reflux symptoms are frequent and tend to escalate with advancing pregnancy, providing another hormonally related context in which to interpret the mechanism of reflux in vivo [7]. For the literature approach the PubMed database can be used as the primary source, selected studies were chosen from the last 10 to 15 years, focused search strings regarding mechanistic logic have been applied [8], e.g. GERD and estrogen, estradiol and lower esophageal sphincter, "estrogen receptor and esophagus, nitric oxide and transient LES relaxation, HRT and reflux symptoms, pregnancy and GERD and hormones, occluding OR tight junction and esophagus and estrogen, human observational and clinical studies and mechanistic human work if of high quality are included; animal or ex vivo [9].

2. Phenotypes of GERD and gender distinctions

GERD is increasingly being described as a spectrum of phenotypes in which the burden of symptoms is not always correlated with an objective finding of endoscopic mucosal injury or the result of ambulatory reflux monitoring. This mismatch is observed in common clinical practice, where on the one hand, patients may complain of frequent heartburn or regurgitation and normal endoscopy, while on the other hand, the opposite may be quite true: erosive disease with fewer symptoms. Modern frameworks (Montreal and Lyon, along with phenotype-based discussions) focused on the separation between the perception of symptoms, reflux burden, and tissue injury aim at a better interpretation of the heterogeneity of GERD [10].

Across populations, symbolized in studies and synthesis papers, it is a neutral finding that women tend to exhibit a higher symptom impact and health-related quality-of-life impairment whereas men tend to exhibit erosive disease characterized by higher rates of complications (a very important pattern that varies greatly by age and hormonal status). For instance, population and clinic-based studies have reported female predominance in the presentation of symptom-driven manifestations of GERD and male predominance in erosive forms but the proportions vary depending on the cohort and the diagnostic criteria [11]. Physiologic testing has also identified hints of sex-based differences in reflux monitoring parameters (impedance/pH parameters) lending further support to the idea that expression of the reflux phenotype can be divergent by sex despite the similarity of associated phenomenon [12].

Interpretation of these differences requires consideration of confounders which affect both reflux and symptom perception including BMI/central obesity, smoking, alcohol, diet patterns, medications (including rehabilitation that affect LES tone), comorbidities (e.g. functional GI overlap) and healthcare seeking behavior. Some large data sets also demonstrate that "risk-factor strength" can be linked with sex such that the same exposure (obesity or smoking for example) may not translate into the same GERD risk in different groups [13]. These considerations are of particular interest in estrogen-focused reviews as estrogen exposure is often correlated with other variables (age, adiposity distribution [14], pregnancy-related behaviors and medications use) that can independently contribute to the development of GERD phenotypes [15].

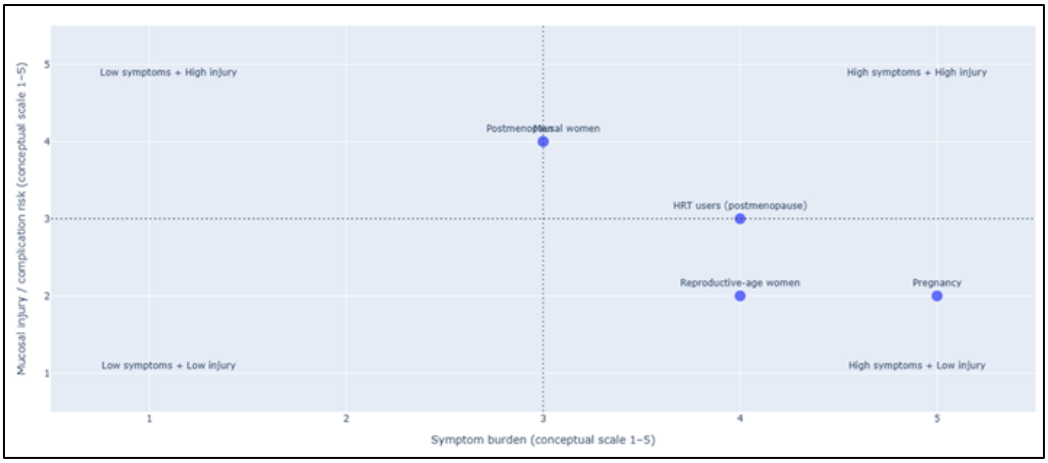

Figure 1 Phenotype tendency and risk of complication on the basis of sex and hormonal status (symptoms vs injury)

3. Basic biochemical processes between estrogen and GERD

3.1. Estrogen receptor signaling in the esophagus and GIT

Estrogen can affect the biology of GERD due to the biological plausibility's of estrogen signaling in the esophagus through estrogen receptors (Ralphi/Ebata) expressed in relevant cell types including the epithelial, immune and smooth muscle-related pathways. Mechanistically, the signaling from estrogen involves both genomic actions (transcriptional regulation after receptor binding) as well as non-genomic or membrane-initiated rapid signaling which can cause changes in later signaling processes in a matter of minutes instead of hours. This is important for GERD because motility, barrier regulation, and inflammatory signaling are "execratory mechanisms" which can be modulated via both fast and slow estrogen dependent mechanisms [16].

3.2. Nitric oxide pathway and LES relaxation

A major central biochemical hypothesis of the association between estrogen and reflux-related events is the nitric oxide (NO) pathway because NO is a major smooth muscle relaxant that plays a role in LES physiology. Experimental data supports that estradiol (E2) can promote LES relaxation via NO-mediated mechanisms, which can plausibly translate clinically to increased basal LES tone and/or more transient LES relaxation increasing reflux episodes and reducing heartburn and regurgitation symptoms.185 This is due to the fact that increased basal LES tone reduces esophageal acid reflux.5 Importantly, the role of NO linked biology is also discussed in a remodeling context and mechanistic work has been done to understand how NO linked signaling may be involved in processes pertinent to the biology of Barrett's (i.e., NO pathway may play roles beyond motility alone) [17].

3.3. Intussusception and tight Junction control of the epithelial barrier.

qḥ e.g. GERD injury is not solely influenced by exposure to acid. An important component is epithelium barrier function in which increased permeability and altered control of tight junctions can lead to increased perception of symptoms as well as susceptibility to erosive injury. Mucosal work performed in the esophagus of humans has described sex-linked differences in gene expression within the tight junction in the diagnosis of GERD, namely, transcripts for genes relating to occluding and claudins, which provides evidence for the theory that barrier biology can be gender-specific and symptom-specific. In parallel, epithelial models' studies show estradiol can be protective to the esophageal epithelial barrier properties during of inflammatory stressors [18,19], reinforcing the arguments of estrogen as a potential mucosal protector, even in a reflux exposed environment. Together, these findings are compatible with the "dual effect" model where the effects of estrogen may work both to increase the incidence of reflux events by hepatoliberalizing actions of estrogen on the RFCs and to moderate the mucosal vulnerability by barriers up, barrier supportive actions [20].

3.4. Anti-inflammatory and immune modulation

Inflammation and neuroimmune signaling resources are gaining momentum in the discussion of modern concepts in GERD particularly in terms of explaining the generation of symptoms and chronicity. Estrogen is able to remodel context-dependent patterns of cytokine and immunity activation it may be able to influence the inflammatory

microenvironment of the esophageal mucosa and downstream signals to sensory system. In esophageal epithelium systems, it has recently been shown that estradiol counteracts certain processes of inflammation experimentally induced by disrupting the barrier.17 As such, estradiol has a proposed protective axis. Broader GERD-focused reviews also emphasize on neuroimmune mechanisms which link mucosal inflammation to the perception of symptoms, as well as provide a conceptual framework in which the immune modulating effects of estrogen could modify both the intensity and severity of symptoms and injury [21].

3.5. Repair and remodeling of oxidative stress.

Chronic exposure to reflux may lead to oxidative stress, DNA damage signal cascade, and inflammatory cascade that contribute to tissue remodeling as well as progression, in susceptible environments, into Barrett's metaplasia to neoplasia. Contemporary mechanistic reviews include reflux-induced oxidative injury networks and inflammatory signal pathways (including PARP-1 Concerning NF kappa B linked pathways) as candidates as a way of explaining progression biology in GERD the induced Barrett's pathways. Complementary reviews are devoted to depict oxidative damage at the epithelium level in reflux situations, in support of oxidative stress representing an attractive "bridge" between repetitive reflux harm and maladaptively fitting remodeling. It is within this landscape that estrogen could be acting on repair programs (restitution, remodeling signals, angiogenic balance) and could potentially influence the long-term phenotype (i.e. symptom-only disease vs. injury prone disease) where measured levels of estrogen have had a trajectory towards the end-determinant histopathological index, but lacked mechanistic studies linking measured levels of estrogen to objective drifting reflux metric and histologic index in human models of reflux disease [22].

Table 1 Biochemical pathways affected by estrogen; these will lead to likely effects on GERD symptoms vs mucosal injury

Mechanism	**Key mediators**	**Predicted effect on symptoms**	**Predicted effect on injury/complications**	**Evidence type (examples)**
ER signaling (genomic + Rapid membrane signaling)	ERα/ERβ, membrane-initiated steroid signaling nodes	Context dependent priming of Motility, Barrier and Inflammatory pathways	Epithelial and immune tone regulation, which is dependent upon the context.	Mechanistic reviews and receptor biology [23].
NO pathway-performance pathway-resting relaxation (LES)	eNOS/nNOS activity, NO bioavailability	↑ LES relaxation / ↑ reflux events → ↑ symptom triggers	There are remodeling effects, which could be the effect of the NO-linked pathways encountered in the Barretts mechanisms.	Experimental physiology + mechanical labor [24].
Tight junction-Epithelial barrier regulation	Occludin, claudins, ZO-1; permeability-related signaling	Barrier disruption symptom amplification Estrogen associated barrier support symptom blunting	Higher barrier can be used to decrease the susceptibility to erosive injury.	Mucosal gene expression + epithelial models H. sapiens [25].
Immune modulation and inflammatory signaling	Cytokine pathways (context-dependent), neuroimmune signaling	May modulate hypersensitivity and symptom intensity	May lessen the severity of injuries and restrain the duration of the inflammatory process.	Model of epithelial + GERD neuroimmune production [26].
Oxidative stress, damage reaction and repair	ROS, DNA damage response, PARP-1/NF-κB, remodeling networks	Symptoms can also be strengthened through sensory pathways via oxidative/inflammatory milieu.	Advocates the metaplastic change and progressive pathological models.	Mechanistic reviews [27].

4. Estrogen, HRT, and GERD

Across the postmenopausal populations, observational evidence indicates that estrogen-containing HRT may be linked to increased reporting of GERD symptoms and/or increased clinical diagnosis of GERD in some datasets, even after adjustment for common covariates in the real world recorded data including age, comorbidities profile, etc. This pattern is biologically plausible because exogenous exposure to estrogen can alter the neuromuscular control of the gastroesophageal junction towards relaxation of smooth muscles which can promote reflux events as the lower esophageal sphincter (LES) barrier is compromised [28].

Mechanistically, one of the ways estrogen effects have been proposed is that estrogen influences the bio-availability of nitric oxide (NO) to enhance inhibitory (relaxant) input in esophageal and LES motor control pathways. Increased nitrergic signal is associated with decreased sphincter tone and an increased ability of the sphincter to allow reflux to occur, which in the clinical setting could lead to heartburn and regurgitation, especially in people who have already risk factors for developing this disease such as a higher BMI, dietary triggers, and delayed clearance.

At the same time, the HRT story is not a one-way street. Some of the evidence is in support of the protective concept wherein estrogen's anti-inflammatory and barrier support properties may lessen the chances of injury progression in a certain context. To illustrate, in a major Swedish cohort design, menopausal hormone therapy also reduced the risk of esophageal adenocarcinoma and gastric cardia adenocarcinoma, relative to nonexistent use, which also indicates that long-term risks of health consequences may be changed due to long-term complications, even in the presence of reflux symptoms. In addition, estrogen pathway modulation is not universally protective: a large real-world analysis of raloxifene (selective estrogen receptor modulator) found higher risk-signal for the development of GER-related outcomes including Barrett's esophagus and stricture contrasting the likelihood of these compound-specific effects, receptor selectivity, dose and host factors all determine the directionality [29]. (Table 2) is a summary of key observational findings associating HRT (and estrogen-pathway therapy) with GERD and outcomes and complications.

Table 2 Significant prospective studies on the effect of HRT (and estrogen-pathway therapy) and GERD outcome

Population	Exposure (type/dose/duration)	Outcome (symptoms/endoscopy/cancer)	Main finding	Study
A big real-world database of postmenopausal women.	HRT exposure (estrogenic-containing regimens in routine care; duration varies by record)	GERD diagnosis and complications associated with GERD.	In real clinical evidence, GERD and complications were more likely with exposure to HRT.	Saleh et al., 2023 [25]
Osteoporotic women of menopausal age.	Raloxifene (estrogenic receptor modulator)	GERD, oesophagus of Barrett, oesophageal fissure.	Exposure to Raloxifene was associated with increased GERD risks and associated complications.	Liu et al., 2023 [26]
Nested case-control analyses on Swedish population-based cohort.	Menopausal hormone therapy (current vs non-use; exposure from registries)	Adenocarcinoma of the oesophagus and gastric cardia.	The use of MHT showed an inverted relationship with the risk of these adenocarcinomas, which proves the opportunity to have a protective effect against long-term problems.	Xie et al., 2021 [27]

5. Pregnancy-Related GERD and Hormonal Processes.

GERD symptoms are commonly reported during pregnancy and they often postpone as the mother gets closer to delivery. A recent systematic review and meta-analysis reported an overall pooled prevalence of about ~41% with a progressive increasing physiologic burden across pregnancy, reported prevalence rates ranging from about ~26% (1st trimester) to 33% (2nd trimester) to 56% (3rd trimester) [30].

The mechanisms are multifactorial but the biochemical contribution is focused ultimately on pregnancy related increases in estrogen and progesterone, which have the capacity to lower LES pressure and so promote reflux permissiveness [31]. Hormone signaling also interacts with the change in motility (slower clearance and altered gastric emptying in some individuals) enhancing the probability of refluxate remaining for a sufficient time to lead to symptom development. Mechanical factors, particularly increased intra-abdominal pressure, may further raise reflux propensity, although the fact that the frequency of symptoms has been found to increase by trimester after trimester clearly allows for an integrated model in which endocrine and biomechanics act together as opposed to being competing explanations.

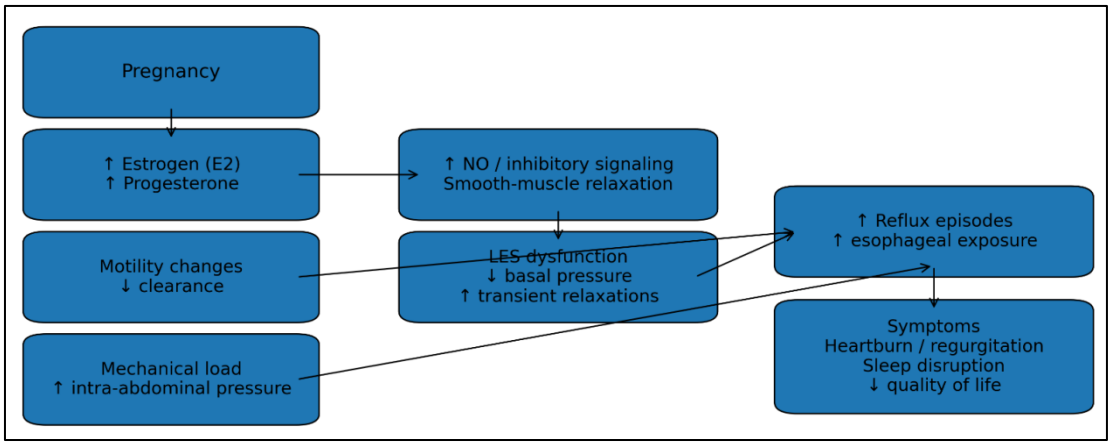

Figure 2 visualizes the pathway logic from pregnancy hormones to reflux episodes and symptom generation

6. Complications based on Estrogen and GERD

6.1. Erosive esophagitis and mucosal injury

The fact that reflux is symptomatic, but not injury-advancing indicates more than the involvement of acid. The balance between epithelial barrier integrity, local inflammatory activation and clearance time can determine if repeated episodes of reflux result in visible erosions. Epidemiologic patterns also support this dissociation of symptoms and injury: In one large group of patients undergoing health screening, reflux esophagitis was more prevalent in men while symptomatic GERD was more prevalent in women, reflecting the reason why symptoms are less than perfect indicators of mucosal injury. This deviation is congruent with a model whereby esophageal reflux permissiveness (symptoms) can be amplified by estrogen-linked pathways and at the same time they are also able to modify mucosal defenses and injury thresholds in a context-dependent manner [32].

6.2. Risk of adenocarcinoma in Barrett and his esophagus.

Progression from the chronic exposure to reflux to the Barrett's esophagus and adenocarcinoma is shaped by repetitive cycles of injuries and repairs, the inflammatory signals and host factors. In low estrogen states (male sex and post-menopause) rates of complications have also often been reported higher than in premenopausal women, although confounding by BMI, smoking and healthcare-seeking behavior are also important. The protective hypothesis is supported by registry-based evidence of potential association of menopausal hormone therapy with reduced risk of esophageal adenocarcinoma and gastric cardia adenocarcinoma with suggestions of estrogen-linked pathways have effects on long-term remodeling and carcinogenesis even in the presence of reflux symptoms [33]. A condensed clinical map between estrogen status and anticipated pattern of GERD is provided in (Table 3).

Table 3 Status of estrogen in clinical settings and anticipated GERD trend

Clinical context	Estrogen status	Symptom tendency	Injury/complication tendency	Notes / mechanistic rationale
Reproductive age	Cyclic, generally higher than post-menopause	Big symptom burden frequently in most cohorts	Adjustable, not necessarily proportional to symptoms	The symptoms can be reflux permissiveness and sensitivity, and the injury is a factor of barrier and clearance [34].
Pregnancy	High and rising across trimesters	Growth of higher order of pregnancy (maximum in 3 rd trimester)	Severe erosive complications were those believed to be rare in comparison with the prevalence of symptoms [30,31].	LES relaxation coupled with hormones and motility and mechanical load enhance the number of refluxes and symptoms [35].
Post-menopause (no HRT)	Lower endogenous estrogen	The symptoms can continue or change under the influence of risk factors	Such patterns have a potential increased susceptibility to injury	Reduced estrogen can change defense/repair ratio; risk of injury is highly adjustable on the basis of BMI and exposures [36].
HRT users	Exogenous estrogen exposure	Is able to augment GERD diagnosis/ symptoms in real-world information	There are datasets that may reduce long-term cancer risk	Dual effect model: Symptom permissiveness through relaxation routes versus potential anti-inflammatory/repair action of complications [37].
Males	Lower estrogen relative to premenopausal females	Injury may be more common than symptoms	More prevalent than in women in certain groups	Separating symptom reporting and mucosal injury, risk factor distribution and biology [38].

7. Impact on Quality of Life

GERD is consistently associated with significant impairment in daily functioning, including sleep disturbance, impaired work performance and diminished overall health-related quality of life, particularly in patients with more severe/permanent symptoms. Quality of life impairment is associated with clinical markers of severity across a variety of settings, including erosive disease grade in a prospective series of data. Population-based analyses also advocate a hypothesis that mental health comorbidity may compound the loss of HRQoL in people with GERD, and that the importance of controlling symptoms of GERD is not only "acid suppression" but more of a general outcome of increased function. A systematic review based on the GI quality-of-life measures of GERD similarly concludes that severe disease is associated with marked QoL reductions in other cohorts [39].

Within the estrogen-centric paradigm of your review, hormone-related variability in symptom expression (for instance during pregnancy or HRT exposure) may be a useful insight to consider when exploring widening variability in the burden of GERD across life stages, and when different and equivalent profiles of objective injury do not result in the identical proportional impact of injury [40].

Across the board of GERD phenotypes, estrogen seems to have a dual and context-dependent role of action. On the one hand, estrogen perhaps promotes reflux occurrences by helping to relax the smooth muscles at an area known as the gastroesophageal junction, which is plausible given that this can cause an increase in transient LES relaxations and symptom expression. On the other aspect, estrogen may dampen the mucosa with epithelial barrier integrity and moderation of inflammatory signaling which might help explain the inconsistency between symptom burden and endoscopic mucosal injury between the sexes, and between hormonal states. These processes are incorporated within a CAD of GERD as an entirety whereby the findings of objective testing factors in the distinction of the true burden of reflux and symptom overlap and functional syndromes [41]. Clinical settings perpetuate this "two edged" pattern. The

risk of the onset of reflux symptoms appears to be positively associated with menopausal hormone therapy (HRT/MHT) in some data-sets, consistent with the notion of a motility/LES-relaxation pathway, but longer-term positive associations with menopausal hormone therapy with a reduced risk of progression to esophageal adenocarcinoma have been suggested in some larger cohorts, consistent with a competing beige hypothesis of mucosal protection and/or changes to the inflammatory remodeling [42]. Pregnancy-associated GERD represents the physiologic model of rising sex hormones combined with mechanical load: based on pooled global estimates, it has been suggested that GERD symptoms affect approximately 41% of pregnancies overall and that the prevalence of GERD symptoms rises by trimester, reaching approximately 56% in the third trimester, which coincides with hormone activities influencing smooth muscles through amplification related to pressure dynamics of late season (third trimester). Finally, outcomes that matter to patients are always of central importance: common symptoms of disease (GERD) are linked to deteriorating quality of sleep and persistence of burden of disease quality of life highlight why hormone-related variability in symptom appearance can be important from clinically relevant perspective in the absence of erosive injury. Future direction: most needed in the field are prospective human studies that simultaneously measured estradiol circulating in blood and concomitant biomarkers, used measures of objective reflux (pH-impedance/manometry), and tracked endpoints of injury/progression (erosive disease, Barrett's, dysplasia) and rigorously controlled adiposity, smoking, medications and comorbidities [43].

8. Conclusion

This narrative review shows that estrogen has a dual and situation-specific effect on the pathophysiology of gastroesophageal reflux disease (GERD). As a result of nitric-oxide-mediated mechanisms, estrogen may increase the lower esophageal sphincter relaxation, which enhances the symptom expression. Simultaneously, estrogen seems to have a protective effect on the esophageal mucosa, namely, strengthening the integrity of the epithelial barrier, altering inflammatory processes, and reducing oxidative stress. The specified dichotomous effect aids in describing the identified difference in the symptom severity and mucosal injury between sexes and hormonal states. This model is supported by clinical situations including pregnancy and menopausal hormone therapy where a high level of estrogen is related to an increased GERD symptom, yet there are some findings to suggest that there is a decreased risks of long term complications when giving hormonal therapies. Such results highlight the fact that GERD is a heterogenous condition, which depends on hormonal and biochemical conditions. A better insight into the processes related to estrogen would contribute to more individualized strategies of diagnosis and treatment. In order to translate these insights into useful clinical and population-health applicability, prospective studies that incorporate the concept of hormonal measurement with objective measures of reflux and mucosal performance are needed.

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