Hormonal Links Between Lipedema and Gynecological Disorders: Therapeutic Roles of Gestrinone and Drospirenone

ABSTRACT

Aims: This study aimed to investigate the pathophysiological mechanisms related to lipedema, starting from the common genetic alteration observed in all cases, which is associated with estradiol receptors (ERα > ERβ). The study explored its connection with normal hormonal fluctuations throughout a woman's life, the effects of xenoestrogens and endocrine disruptors on estradiol metabolism, and, most notably, its strong association with gynecological disorders in many cases. These disorders are linked to increased production of aromatase, 17β-HSD1, and progesterone resistance, with elevated 17β-HSD2 levels, leading to conditions such as adenomyosis, endometriosis, and miomatosis. Based on these findings, the study proposes the potential therapeutic use of progestins, such as gestrinone and drospirenone, as treatment options for women with lipedema.

Study design: Narrative literature review.

Methods: A narrative literature review was conducted using the PubMed electronic database. Complementary studies were identified manually using Google Scholar and through citations of relevant authors.

Results: Evidence highlights a strong influence of estradiol in the pathophysiology of lipedema, with the imbalance of estradiol receptors (ERα > ERβ), known as the common pathway, as the underlying mechanism. A higher proportion of ERα in adipose tissue triggers a pathological response leading to inflammation, hypertrophy, microangiopathy, immune dysfunction, and fibrosis. Physiological fluctuations in estradiol levels, along with hormonal responses to behavioral and dietary changes, are the most common factors driving lipedema progression. As a result, dietary modifications, specific nutritional strategies, and lifestyle changes remain the primary therapeutic approach. However, in some cases, lipedema shares common pathophysiological mechanisms with estrogen-dependent gynecological conditions. In these cases, progestins, particularly gestrinone and drospirenone, may represent potential therapeutic options for lipedema due to their ability to modulate specific hormonal pathways. Both drugs exhibit anti-inflammatory properties and counteract progesterone resistance by increasing PRβ expression and the production of 17β-hydroxysteroid dehydrogenase 2 (17β-HSD2). This enzyme facilitates the metabolism of estradiol into less potent estrogens, such as estrone, thereby reducing the pathological effects of estradiol on adipose tissue. Additionally, gestrinone reduces ovarian aromatase activity and 17β-HSD1 expression.

Conclusion: The study emphasizes the hormonal nature of lipedema and its connection to gynecological conditions, underlining the therapeutic potential of progestins such as gestrinone and drospirenone. By modulating hormonal imbalances, these medications represent promising strategies for managing lipedema and improving patient outcomes. However, the study relies on a narrative review, which limits the strength of the conclusions due to the lack of systematic analysis or meta-analytical approaches. Further research, including well-designed clinical trials and experimental studies, is needed to validate these findings and expand treatment options.

Keywords: *Lipedema, Genital Diseases, Female, Hormone Replacement Therapy, Gestrinone, Drospirenone*

1. INTRODUCTION

Lipedema is a chronic, estrogen-dependent hormonal disorder characterized by disproportionate, painful fat accumulation in women. It is mediated by an imbalance between alpha and beta estradiol receptors in adipose tissue, leading to inflammation and adipose tissue dysfunction. No pharmacological treatment or cure is currently available (Al-Ghadban, Teeler, & Bunnel, 2021). The global prevalence of lipedema is estimated at 11%, although variations exist due to discrepancies in diagnostic criteria. In Brazil, an estimated 12.3% of female patients meet the criteria for lipedema (Amato et al., 2022), while in the United States, the prevalence is reported as 1 in 9 adult women (Buck & Herbst, 2016). In Europe, prevalence estimates range from 0.06% to 39%. These discrepancies often arise due to errors in study design, including misclassification with lymphedema, as well as the subjective nature of diagnostic criteria.

First described in adult women in 1940 by Allen and Hines, lipedema differs from obesity due to its resistance to caloric deficits, including dieting, physical exercise, and even bariatric surgery (Allen & Hines, 1940; Wold, Allen & Hines, 1951). It also differs from lymphedema, as it presents symmetrically and spares the hands and feet (negative Stemmer sign). Misuse of the terms “lymphedema” and “lipedema” can lead to misdiagnosis, affecting prognosis and treatment decisions (Greene & Sudduth, 2021).

Recent studies highlight a hormonal component in lipedema’s pathophysiology, particularly the distribution of estradiol receptors in adipose tissue. An imbalance between alpha and beta estradiol receptors contributes to adipocyte hypertrophy, inflammation, and vascular, immunological, and lymphatic dysfunction (Katzer et al., 2021). Furthermore, lipedema shares pathophysiological mechanisms with gynecological disorders such as endometriosis, adenomyosis, and uterine fibroids, particularly in relation to progesterone resistance. This resistance is associated with reduced 17β-HSD type 2, increased aromatase and 17β-HSD type 1, leading to local estradiol accumulation without proper metabolism. Given these hormonal similarities, synthetic progestins such as gestrinone and drospirenone have been proposed as potential therapeutic options for lipedema (Katzer et al., 2021; Al-Ghadban et al., 2024).

The primary clinical goal in lipedema treatment is not aesthetic improvement but the reduction of pain, edema, and inflammation, as well as halting disease progression. Currently, the only effective treatments include anti-inflammatory diets (such as ketogenic or Mediterranean diets) and liposuction (Herbst et al., 2021). While no definitive cure exists, ongoing research into novel therapeutic strategies offers hope for affected individuals.

The aim of this review its synthesize current scientific knowledge on lipedema, addressing its prevalence, pathophysiological mechanisms, clinical presentation, differential diagnosis, and therapeutic options. By exploring its hormonal and gynecological associations, this work seeks to enhance diagnostic accuracy and guide the development of effective treatment strategies, ultimately improving patient outcomes.

2. METHODS

Studies for this narrative literature review were identified using various search strategies conducted on PubMed (https://pubmed.ncbi.nlm.nih.gov/) on September 16, 2024, as detailed in Table 1. In addition to these strategies, studies were manually identified from the same database, Google Scholar (https://scholar.google.com.br/), and citations from relevant authors.

Database	Search Strategies	Nº
PUBMED	(Lipedema[MeSH Terms] OR Lipedema OR Lipoedema OR Lipolymphedema) AND (Gestrinone[MeSH Terms] OR Gestrinone OR Dimetriose OR Nemestran OR drospirenone OR Progestins[MeSH Terms] OR Gestagen OR Progestagen OR Progestagenic OR Progestational OR Progestin OR Progestogen)	2
	("Genital Diseases, Female"[MeSH Terms] OR Female Genital Disease*[title] OR Gynecologic Disease[title]) AND (Gestrinone[MeSH Terms] OR Gestrinone[title]) AND (Therapeutics[MeSH Terms] OR Therapeutic)	120
	(Lipedema[MeSH Terms] OR Lipedema[Title/Abstract] OR "Fat legs"[Title/Abstract] OR "fat legs"[Title/Abstract] OR "orthostatic edema"[Title/Abstract]) AND ("Estrogens"[MeSH Terms] OR "Estradiol"[MeSH Terms] OR Estradiol[Title/Abstract] OR "Progesterone"[MeSH Terms] OR	174

	Progesterone[Title/Abstract] OR Hormones[Title/Abstract] OR "Aromatase"[MeSH Terms] OR Aromatase[Title/Abstract] OR "Adipose Tissue"[MeSH Terms] OR "Adipocytes"[MeSH Terms] OR Inflammation[MeSH Terms] OR Metabolism[MeSH Terms] OR Adipocytes[Title/Abstract]OR Inflammation[Title/Abstract] OR Metabolism[Title/Abstract])	
Google Scholar	Lipedema AND (gestrinone OR dimetriose OR Nemestran OR drospirenone OR Progestins OR Progestogen)	80
Total		**376**

Table 1. Search strategies used on Medline/PubMed

3. RESULTS AND DISCUSSION

Different types of studies were included that address the topics listed in this review, as described below, with their respective totals: Case Reports (n = 2), Clinical Trial (n = 2), Randomized Controlled Trial (n = 3), Comparative Study (n = 1), Consensus Guideline (n = 1), Cross-sectional (n = 1), Cross-Sectional Studies (n = 1), Experiment study (n = 3), Experiment study (in vitro) (n = 2), Observational Study (n = 1), Population survey (n = 1), Practice Guideline (n = 1), Prospective comparative study (n = 1), Qualitative study (n = 1), Retrospective Studies (n = 1), Review (n = 17), Systematic Review; Meta-Analysis (n = 1). In addition, complementary sources were included, such as Book (n = 1), Chapters in book (n = 1), Conference Paper (n = 1), Educational Video (n = 1), Topic (n = 2). The analysis of the included studies revealed a lack of strong evidence to draw clear conclusions on this topic. The heterogeneity of these studies, which included one systematic review and three randomized controlled trials, makes direct comparison of results difficult. This suggests the need for additional research, particularly controlled clinical trials and systematic reviews.

3.1 Lipedema's Pathophysiological Hypothesis

The pathophysiology of lipedema involves a complex interplay of genetic, hormonal, and environmental factors, with multiple interconnected pathways contributing to the development and progression of the condition (Katzer et al., 2021).

An increased expression of alpha estradiol receptors relative to beta estradiol receptors in adipocytes is consistently observed in all cases of the disease, referred to as the "Common Pathway." Additionally, three other pathways contribute to the onset and progression of lipedema: gynecological factors, behavioral influences, and hormonal fluctuations throughout a woman's life (Figure 1).

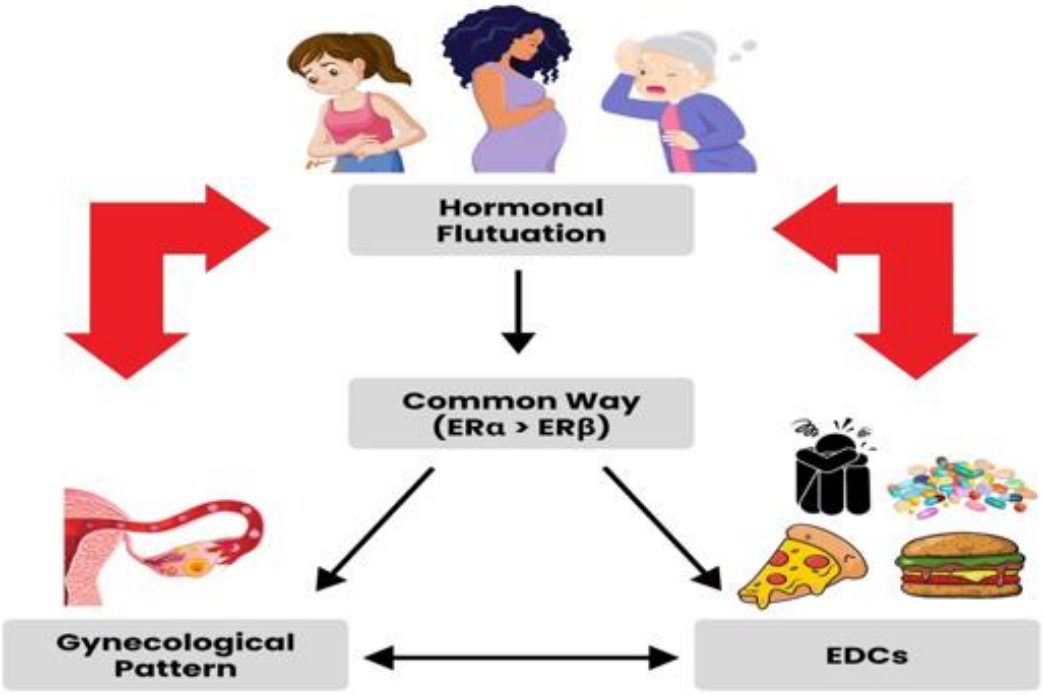

Fig 1: The interconnection among, Common Pathway (genetic condition that leads to increased expression ERα and a reduction ERβ in all cases) hormonal fluctuation, gynecological patterns and endocrinal disruptors (EDCs).

Figure 1 Shows the interconnection among, Common Pathway (genetic condition that leads to increased expression ERα and a reduction ERβ in all cases) hormonal fluctuation, gynecological patterns and endocrinal disruptors (EDCs). All cases of lipedema originate from the common pathway. The periods of disease worsening are associated with the three additional pathways, each acting individually or in combination, intertwining and overlapping in their causes.

These pathways often overlap but can provide valuable insights into clinical history, highlighting suggestive signs of the disease. When combined with a physical examination, this approach enhances diagnostic accuracy, facilitates a more precise estimation of disease incidence, and helps reduce the risk of underdiagnosis.

All the pathways are interconnected within the complex spectrum of lipedema. Identifying pathophysiological associations with gynecological disorders could pave the way for new therapeutic possibilities, particularly with the use of progestogens such as gestrinone and drospirenone. In a condition lacking defined and effective pharmacological treatments, these developments could offer hope to many women who endure the physical and psychological burdens of the disease.

3.2 Common Pathway Hypothesis

Lipedema is proposed to be a polygenic disease with hormonal characteristics regulated by the actions of estradiol, resulting in fat inflammation. This condition is characterized by increased expression of ERα in the adipose tissue of specific areas, particularly in the lower limbs, presenting symmetrically yet disproportionately. A genetic imbalance between ERα and ERβ, known as the 'common pathway,' is consistently observed in all cases, a phenomenon referred to as the "common pathway".

Estradiol plays a critical role in the distribution and metabolism of adipose tissue, and disruptions in its signaling can contribute to the asymmetrical fat deposition observed in lipedema (Pedersen et al., 2004). It regulates adipocyte proliferation, differentiation, and lipid metabolism, and disturbances in these processes result in one of the hallmark features of the disease: the disproportionate yet symmetrical accumulation of fat, particularly in the lower limbs (Katzer et al., 2021).

In subcutaneous adipose tissue, the increased ratio of alpha estradiol receptors (ERα) to beta estradiol receptors (ERβ) disrupts estradiol signaling pathways. This alteration promotes adipocyte growth and expansion, as well as increases local inflammation and fibrosis (Poojari, Dev & Rabiee, 2022). These changes are considered key contributors to the abnormal fat accumulation and irregular growth of adipose tissue observed in lipedema (Katzer et al., 2021).

Furthermore, estradiol influences the function of lipoprotein lipase (LPL), an enzyme responsible for fatty acid storage in cells, leading to increased fat deposition. This effect is primarily mediated by ERα and plays a critical role in activating the peroxisome proliferator-activated receptor gamma (PPAR-γ), which promotes adipocyte differentiation and lipid accumulation (Katzer et al., 2021).

In the lymphatic system, estradiol induces vascular and lymphatic alterations, increasing vascular permeability and exacerbating fluid accumulation and edema (Katzer et al., 2021; Al-Ghadban et al., 2024). Additionally, overactivation of the ERα receptor, driven by elevated estradiol levels, can lead to lymphangiogenesis by promoting the expression of related genes such as VEGF-D and VEGFR-3 (Bardhi et al., 2024).

Thus, the common pathway, present in all cases of lipedema, underscores the genetic predisposition and illustrates how adipose, lymphatic, and vascular tissues pathologically respond to the local actions of estradiol.

3.3 Hormonal Fluctuation

Evidence suggests that lipedema is influenced by genetic factors that alter the distribution and proportion of estradiol receptors. However, the primary regulatory factor appears to be the levels of estrogen in the body (Bessesen et al., 2015). Lipedema is frequently observed during periods of significant hormonal changes in a woman’s life, such as puberty, pregnancy, and menopause, which play a critical role in the onset and progression of the condition and its symptoms (O’Sullivan et al., 2001; Reich-Schupke et al., 2017; Lipedema Foundation, 2023).

During puberty, the substantial increase in estradiol levels can lead to changes in the distribution of estrogen receptors within adipose tissue, resulting in localized increases in estrogen activity. This stage is often when the first symptoms of lipedema become apparent.

Clinically, during pregnancy, women with lipedema experience significant worsening of the disease, characterized by increased edema, pain, and substantial weight gain. Many women report difficulty returning to their pre-pregnancy weight and regular fat distribution, with these challenges being more pronounced than in women without lipedema.

However, menopause may represent the stage in a woman's life with the most significant worsening of lipedema, which presents a paradox, as menopause is characterized by the cessation of ovarian estradiol production. During the menopausal transition, the pronounced fluctuations in estradiol levels exacerbate the symptoms of lipedema, potentially worsening the disease. This stage is also associated with other conditions, such as adenomyosis (Bessesen et al., 2015).

In menopause, the absence of estradiol contributes to increased weight gain through both direct and indirect mechanisms affecting adipocytes. Beyond the lack of estradiol itself, untreated menopausal symptoms such as insomnia, fatigue, sarcopenia, a decline in basal metabolic rate, and an increased orexigenic effect can collectively promote a caloric surplus, further contributing to fat accumulation. Additionally, the absence of estradiol leads to dysregulation of adipocyte functions, exacerbating the pathological processes underlying lipedema and complicating disease management.

3.4 Behavioral Patterns and Endocrine Disruptors (EDCS)

A sedentary lifestyle, chronic stress, corticosteroid use, combined oral contraceptives, and certain dietary components—such as gluten, lactose, and processed carbohydrates—are recognized contributors to the onset and progression of lipedema (Annunziata et al., 2024). Xenoestrogens, which mimic or interfere with endogenous estrogens, bind to estrogen receptors (ERs) and cause hormonal dysregulation by simulating excess estradiol in the body (Lee et al., 2013). These compounds interact with ERα and ERβ receptors, as well as membrane-bound receptors like GPER, disrupting hormonal homeostasis and promoting estrogen-dependent diseases, including endometriosis and breast cancer (Szukiewicz, 2023, Nagasaki et al., 2009)

When binding to alpha estradiol receptors with greater affinity and potency than estradiol itself, xenoestrogens trigger inflammatory pathways in adipose tissue, exacerbating conditions like lipedema (Hampl, Kubátová & Stárka, 2014; Zeitoun et al., 1998). Compounds such as bisphenol A (BPA) and phthalates disrupt estradiol signaling by either mimicking or antagonizing its effects, leading to abnormal fat accumulation, fibrosis, and inflammatory responses (Deluca et al., 2005; Jung et al., 2014). This is particularly relevant in lipedema, where affected adipocytes show heightened sensitivity to estrogenic stimuli, promoting the disproportionate fat deposition characteristic of the disease. Furthermore, BPA and certain pesticides activate aromatase, leading to an increase in local estradiol production—a mechanism linked to conditions such as breast cancer and endometriosis (Patel, 2017; Mori et al., 2015).

Additionally, dietary phytoestrogens, while structurally similar to estradiol, can act as endocrine disruptors by binding to estrogen receptors and modulating gene expression. They can inhibit enzymes like 17β-hydroxysteroid dehydrogenases (17β-HSD), which play key roles in converting weak estrogens to more potent forms, further altering adipose tissue metabolism and local hormone production (Deluca et al., 2005; Hilborn, Stål & Jansson, 2017). Altered activity of 17β-HSD1 and 17β-HSD2 enzymes in lipedema contributes to enhanced estradiol retention in adipocytes, exacerbating inflammation and tissue remodeling through the dysregulation of matrix metalloproteinases (MMPs), such as MMP14 (Kruglikov, Joffin & Scherer, 2020).

Given these findings, therapeutic strategies should focus on minimizing exposure to endocrine-disrupting chemicals (EDCs), implementing anti-inflammatory dietary interventions, and exploring targeted hormonal therapies aimed at restoring hormonal balance and mitigating adipose tissue dysfunction in lipedema.

3.5 Gynecological Pattern

Although lipedema predominantly affects women, there are rare reports of the disease occurring in males with Klinefelter's syndrome (Bertlich et al., 2021), further supporting the role of estradiol in the pathophysiology of lipedema. Additionally, studies have identified correlations between lipedema and various gynecological disorders (Figure 2). Seefeldt et al. (2023) reported that 43% of women with lipedema experienced menstrual irregularities. Similarly, Patton et al. (2024) observed that among women with lipedema, 17% had polycystic ovary syndrome (PCOS), 15.3% had uterine myomas, 11.5% presented with breast cysts, and 4.1% had endometriosis.

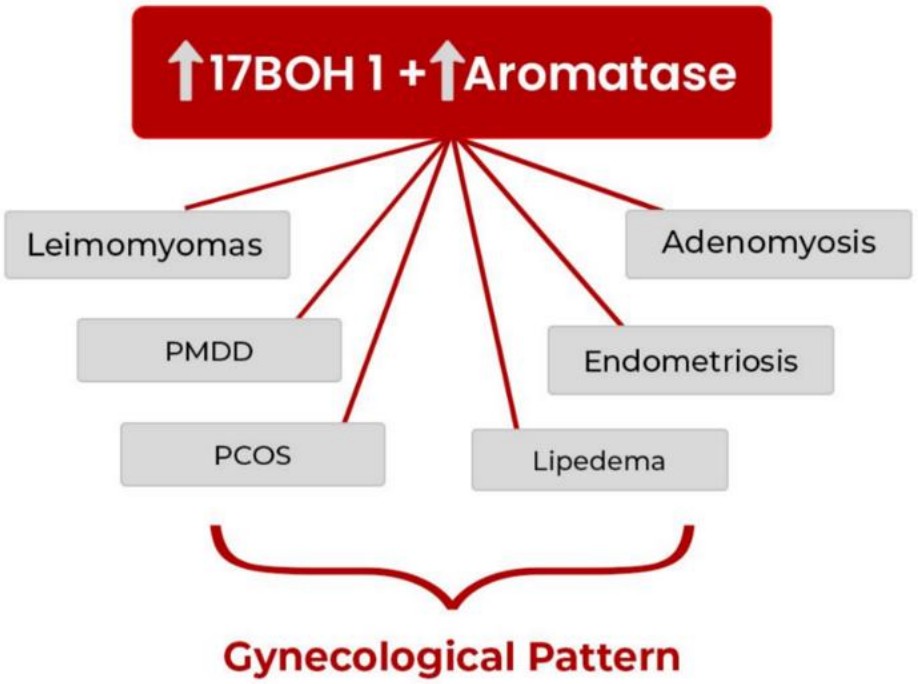

Figure 2. The umbrella of gynecological diseases that share the same enzymatic pathophysiological mechanisms leading to increased estradiol action leading to the gynecological pattern.
(PMDD: Premenstrual Dysphoric Disorder; PCOS: Polycystic Ovary Syndrome.)

It is essential to consider the shared pathophysiological mechanisms between lipedema and gynecological conditions such as endometriosis, adenomyosis, and myomatosis, particularly regarding the roles of aromatase, 17β-hydroxysteroid dehydrogenase (17β-HSD types 1 and 2), and peripheral resistance to progesterone action (Bulun et al., 2023; Delvoux et al.,Zeitoun et al., 1998; Zeitoun et al., 1999). The role of 17β-Hydroxysteroid Dehydrogenases is already well studied and proposed in other estrogen-sensitive diseases, such as breast cancer (Nagasaki et al., 2009), highlighting their importance in estradiol metabolism in the development of these pathologies.

In these conditions, aromatase plays a significant role by increasing local estrogen production. Additionally, the presence of prostaglandin E_1 (PGE_1), often elevated due to inflammatory responses, amplifies estrogen synthesis, creating a feedback loop that exacerbates the condition. A similar mechanism is observed in lipedema (Leyendecker et al., 2009).

The imbalance between alpha and beta estrogen receptors in adipocytes leads to exaggerated estradiol signaling, which promotes fat accumulation and local inflammation. Women with lipedema exhibit heightened aromatase activity in their adipose tissue, perpetuating this cycle of fat accumulation and inflammation (Katzer et al., 2021).

Another shared mechanism involves dysregulation in the enzymatic conversion of estrone (E_1) and estradiol (E_2) by 17β-HSD. Specifically, increased 17β-HSD1 activity, which converts E_1 to E_2, coupled with reduced 17β-HSD2 activity, which converts E_2 to E_1, results in elevated local E_2 levels. This imbalance promotes estradiol retention, driving the growth of endometriotic lesions and contributing to the development of adenomyosis and myomas. A similar process is likely to occur in lipedema, where elevated localized estradiol levels in adipose tissue exacerbate its progression.

In lipedema, resistance to progesterone in adipose tissue has also been documented (O'Brien et al., 1998). This resistance leads to reduced 17β-HSD2 expression, increased activity of aromatase and 17β-HSD1, and a failure to inhibit aromatase, which is abundantly expressed in adipose tissue. These shared mechanisms underscore the significant pathophysiological parallels between lipedema and gynecological diseases.

4 GESTRINONE E DROSPIRENONE IN LIPEDEMA'S TREATMENT

4.1 Gestrinone

Gestrinone is widely used in Europe as a progestogenic steroid to manage symptoms of endometriosis, including menstrual and pelvic pain. It has demonstrated positive results, with efficacy comparable to other treatments such as danazol and leuprolide acetate (Brown et al., 2012). Additionally, it is used in the treatment of other estrogen-sensitive conditions, such as uterine myomatosis and adenomyosis (Coutinho & Gonçalves, 1989; Coutinho et al., 1986).

The mechanism of action of gestrinone is complex. It is a synthetic progestogen belonging to the 19-nortestosterone family, with moderate androgenic activity, weak anabolic properties, antigonadotropic effects, and antiestrogenic effects on the endometrium. It exerts strong progestogenic activity through the β progesterone receptor (PRβ), leading to increased expression of 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) and inhibition of 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) and ovarian aromatase (DRUGBANK, 2024; Canivilo & Caseri, 2023).

In endometriosis, these effects contribute to controlling lesion growth by overcoming progesterone resistance, a key pathophysiological mechanism of the disease, through increased expression of 17β-HSD2 (Grada & Phillips, 2017). Furthermore, gestrinone reduces the expression of aromatase and 17β-HSD1 in the ovaries, thereby increasing the conversion of estradiol (E2) into estrone (E1) or limiting the transformation of E1 back into E2 (Figure 3).

This dual inhibition mechanism may also prove beneficial in controlling lipedema by promoting the metabolism of estradiol, a more potent estrogen, thereby reducing its local concentrations and mitigating the hyperactivation of α estrogen receptors (ERα) in adipose tissue (Renke et al., 2024). Additionally, as a progestin, gestrinone acts on PRβ receptors to increase the expression of 17β-HSD2.

In the treatment of lipedema, gestrinone offers several potential benefits, particularly when associated with gynecological conditions and administered via gynecological routes (Renke et al., 2024). Its ability to reduce ovarian estradiol production and enhance its metabolism facilitates local elimination and may help alleviate lipedema symptoms.

The proposed benefits of gestrinone do not appear to stem from its androgenic or anabolic effects, nor from its central antigonadotropic activity. Instead, its efficacy seems to be linked to its capacity to support estradiol metabolism, promote fat clearance, reduce ERα activation, and control adipocyte inflammation caused by estradiol. Further studies are required to validate this hypothesis.

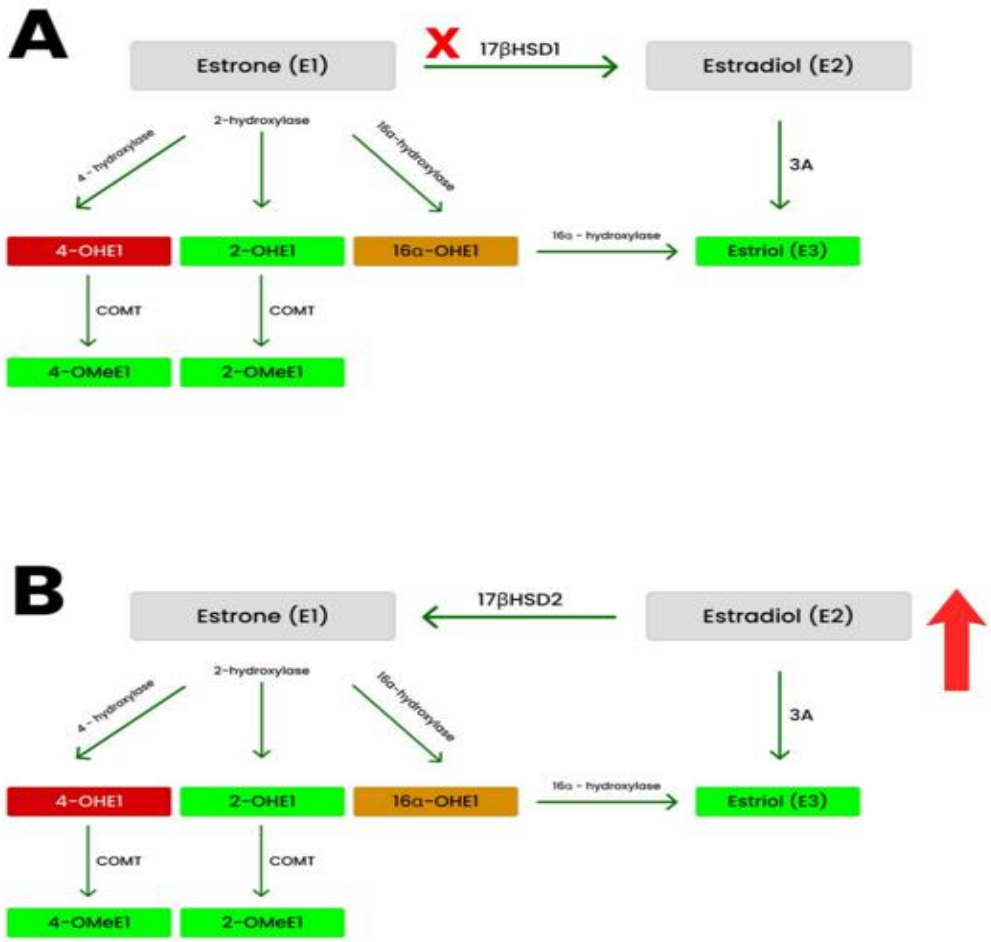

Figure 3 Conversion processes between estrone (E_1) and estradiol (E_2), with dysfunction in the 17β-HSD enzymes.
*Source: Adapted by the authors (*Physicians Lab, 2024).
(COMT: Catecol-O-Metiltransferase; OHE1: hydroxyestrone)

4.2 Drospirenone

Drospirenone, a synthetic progestogen with antimineralocorticoid and antiandrogenic properties, has been studied for its effects on adipose tissue (Caprio et al., 2011; Tankó & Christiansen, 2005; Karakus et al., 2012), which may have potential implications for conditions such as lipedema.

In addition to its ability to regulate ovarian estradiol production through the central antigonadotropic effects common to all progestins, drospirenone exhibits anti-inflammatory properties by binding to progesterone receptors (PRs), particularly the beta subunit. This interaction reduces the production of pro-inflammatory cytokines such as TNF-α and IL-1β, while increasing the production of anti-inflammatory cytokines such as IL-10 (Fedotcheva et al., 2022). Furthermore, medical literature suggests that drospirenone has an anti-adipogenic effect, inhibiting adipocyte differentiation and triglyceride accumulation in both pre-adipocyte cell lines and primary human pre-adipocytes (Caprio et al., 2011). This effect is mediated by its antagonism of mineralocorticoid receptors (MRs), independent of glucocorticoid, androgen, or progesterone receptor activity (Caprio et al., 2011).

In addition to its anti-inflammatory actions, drospirenone reduces sodium and water retention by blocking aldosterone activity, acting similarly to spironolactone. These properties suggest potential therapeutic effects in lipedema, including reducing the inflammatory response, alleviating lymphatic edema, and modulating estradiol activity, particularly by targeting progesterone resistance.

Studies in postmenopausal women receiving hormone therapy with drospirenone and 17β-estradiol have demonstrated alterations in adipose tissue distribution and adipokine levels (Tankó & Christiansen, 2005). For instance, treatment with drospirenone has been associated with reductions in central fat mass, modifications in adipokine secretion, and decreased

levels of adiponectin. These changes could potentially influence metabolic and cardiovascular risk factors (Tankó & Christiansen, 2005; Karakus et al., 2012).

Drospirenone may also play a role in preventing fibrosis. Aldosterone is known to promote collagen production and tissue remodeling, contributing to chronic inflammation and fibrosis. The antagonism of aldosterone activity is already employed as a therapeutic strategy in conditions such as heart failure (Miller, 2007). In lipedema, excessive estradiol activity through overexpressed ERα receptors leads to increased local collagen production, resulting in the expansion and hardening of the extracellular matrix, which contributes to adipose tissue fibrosis (Al-Ghadban et al., 2024). Therefore, blocking aldosterone may offer therapeutic benefits, particularly in the advanced stages of lipedema.

These findings suggest that drospirenone may influence the characteristics of adipose tissue and offer potential therapeutic value in lipedema. However, its direct effects on lipedema have not been extensively studied.
In conclusion, while drospirenone shows promise in modulating adipose tissue dynamics, further research is essential to fully understand its impact on lipedema and other adipose tissue-related disorders.

5 CONCLUSION

The objective of this study was to explore the relationship between lipedema and gynecological diseases, such as endometriosis, adenomyosis, and polycystic ovarian syndrome (PCOS), with a focus on underlying hormonal mechanisms and the therapeutic potential of progestins, such as gestrinone and drospirenone. This narrative review highlights the importance of investigating these hormonal connections to propose new therapeutic options and contribute to a better understanding of the disease.

The findings suggest that lipedema shares pathophysiological pathways with estrogen-dependent gynecological conditions, with particular emphasis on the roles of aromatase and 17β-hydroxysteroid dehydrogenase (17β-HSD). These enzymes increase estrogen production in affected tissues and alter the expression of estrogen receptors (ERα and ERβ), promoting fat accumulation and inflammation—hallmarks of lipedema. Furthermore, the progesterone resistance observed in lipedema, as well as in conditions like endometriosis, supports the hypothesis that progesterone plays a significant role in the development of lipedema, positioning it as a potential therapeutic target.

Despite the contributions of this study, certain limitations must be acknowledged, including the inability to draw definitive therapeutic conclusions. While a narrative review is valuable for consolidating existing knowledge, it does not allow for a quantitative analysis of data. Additionally, the scarcity of detailed primary studies on specific hormonal mechanisms in lipedema and the efficacy of progestins limits the generalizability of these findings. Nonetheless, this study offers an integrated perspective on the hormonal factors involved in lipedema and underscores the importance of exploring targeted interventions.

Further research is needed to validate these findings through clinical trials and experimental models. We recommend investigating the molecular mechanisms of lipedema, with particular attention to alterations in estrogen signaling and progesterone resistance. Controlled clinical studies evaluating the efficacy of gestrinone and drospirenone in managing lipedema are also essential to validate these therapeutic options. Such investigations could not only expand the understanding of lipedema pathophysiology but also pave the way for more effective and personalized therapeutic strategies, benefiting women who face this challenging condition and guide professionals specifically gynecologists and endocrinologists to the correct management of Lipedema.

DISCLAIMER (ARTIFICIAL INTELLIGENCE):

The authors declare that generative AI was used solely during the final stage of manuscript preparation (post-writing) and exclusively for linguistic refinement in the English language (Name: ChatGPT; Version: GPT-4; Model:OpenAI's Large Language Model; Source:OpenAI - https://openai.com). No original text was generated or substantively edited by the AI.

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