Minireview Article

The Hormonal Nexus of Lipedema and Gynecological Conditions: Therapeutic Insights with Gestrinone and Drospirenone

ABSTRACT

Aims: This study aimed to investigate the pathophysiological mechanisms underlying lipedema, focusing on the disproportion of estradiol receptors (ERα > ERβ) and its association with gynecological conditions. Additionally, the therapeutic potential of progestins, such as gestrinone and drospirenone, was explored 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 hormonal influence in the pathophysiology of lipedema, with a key role played by the imbalance of estradiol receptors (ERα > ERβ). This hormonal dysregulation promotes fat accumulation, inflammation, and fibrosis in adipose tissue. Furthermore, lipedema shares common pathophysiological mechanisms with gynecological conditions such as endometriosis and adenomyosis. Progestins, including gestrinone and drospirenone, were identified as potential therapeutic options for lipedema due to their ability to modulate hormonal pathways. Both medications exhibit anti-inflammatory properties and address progesterone resistance by increasing the expression of PRβ and the production of 17β-hydroxysteroid dehydrogenase 2 (17β-HSD2). This enzyme facilitates the metabolism of estradiol into less potent estrogens, such as estrone, contributing to a reduction in the pathological effects of estradiol on adipose tissue.

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 addressing key hormonal imbalances, these medications represent promising strategies for managing lipedema and improving patient outcomes. Further research is needed to validate these findings and expand treatment options.

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

1. INTRODUCTION

In Brazil, an estimated 12.3% of female patients meet the criteria for lipedema (Amato et al., 2022). In the United States, the prevalence is reported as 1 in 9 adult women (Buck & Herbst, 2016). In Europe, estimates of prevalence range from 0.06% to 39%. Globally, the incidence of the disease is significant, affecting over 11% of adult women (Christoffersen & Tennfjord, 2023; Katzer et al., 2021). However, discrepancies in reported prevalence arise due to errors in group analyses; many studies include women with lymphedema, which can lead to overestimated incidence rates. Additionally, the subjective nature of diagnostic criteria contributes to this variability. Understanding the pathophysiological mechanisms is

therefore of critical importance, as it can help clinicians identify diagnostic patterns in patient history and guide accurate diagnosis.

First described in adult women in 1940 by Allen and Hines, lipedema differs from common obesity due to its resistance to dieting and physical exercise. Even after bariatric surgery, the condition persists, highlighting its lack of response to caloric deficits (Allen & Hines, 1940; Wold, Allen & Hines, 1951).

Lipedema also differs from lymphedema, as it is characterized by its symmetrical presentation and the absence of involvement of the hands and feet (Stemmer sign). The terms “lymphedema” and “lipedema” are often used interchangeably to describe excessive growth of the legs, regardless of the underlying etiology. However, accurate diagnosis is crucial, as the prognosis and treatment of these conditions vary significantly (Greene & Sudduth, 2021).

Recent studies suggest a hormonal component in the pathophysiology of lipedema, focusing on the distribution of estradiol receptors. Alterations in the distribution patterns of beta and alpha estradiol receptors in adipose tissue have been identified, with an increased presence of alpha receptors relative to beta receptors. This imbalance results in a pathological response to estradiol within the adipose tissue, leading to hypertrophy and inflammation of adipocytes, as well as vascular, immunological, and lymphatic dysfunctions. Consequently, the disease is characterized by the painful and disproportionate accumulation of subcutaneous adipose tissue (Katzer et al., 2021).
Additionally, evidence suggests a potential link between lipedema and gynecological disorders, such as endometriosis and adenomyosis, due to shared hormonal pathophysiological mechanisms. This raises the possibility of utilizing progestogens, such as gestrinone and drospirenone, as potential treatments (Katzer et al., 2021; Al-Ghadban et al., 2024).

It is important to emphasize that the primary clinical goal of lipedema treatment is not aesthetic improvement but rather addressing physical and psychological pain, edema, and swelling, as well as the potential for regression of disease progression. Currently, the only effective treatments include anti-inflammatory diets (such as ketogenic or Mediterranean diets) and liposuction (Herbst et al., 2021). While there is no cure for lipedema to date, the exploration of new treatment possibilities brings significant hope for affected individuals.

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The aim of this study is to briefly review the scientific literature on lipedema, addressing its prevalence, pathophysiological mechanisms, clinical presentation, differential diagnosis, and available therapeutic approaches. By synthesizing the existing evidence, this review seeks to deepen the understanding of the unique characteristics of this condition, explore its hormonal and gynecological associations, and highlight effective treatment strategies. The goal is to contribute to the development of more accurate diagnostic criteria and therapeutic interventions that can reduce the physical and psychological burden of lipedema on patients.

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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.

Articles were initially screened based on their titles and abstracts. Those deemed eligible were retrieved for a comprehensive full-text review.

Table 1. Search strategies used on Medline/PubMed

	Search Strategies	Nº
Search 1	(Lipedema[mh] OR Lipedema OR Lipoedema OR Lipolymphedema) AND (Gestrinone[mh] OR Gestrinone OR Dimetriose OR Nemestran OR drospirenone OR Progestins[mh] OR Gestagen OR Progestagen OR Progestagenic OR Progestational OR Progestin OR Progestogen)	2
Search 2	("Genital Diseases, Female"[mh] OR Female Genital Disease*[ti] OR Gynecologic Disease[ti]) AND (Gestrinone[mh] OR Gestrinone[ti]) AND (Therapeutics[mh] OR Therapeutic)	120
Search 3	(Lipedema[mh] OR Lipedema[tiab] OR "Fat legs"[tiab] OR "fat legs" OR "orthostatic edema"[tiab]) AND ("Estrogens"[mh] OR "Estradiol"[mh] OR Estradiol[tiab] OR "Progesterone"[mh] OR Progesterone[tiab] OR Hormones[tiab] OR "Aromatase"[mh] OR Aromatase[tiab] OR "Adipose Tissue"[mh] OR "Adipocytes"[mh] OR	174

	Inflammation[mh] OR Metabolism[mh] OR Adipocytes[tiab] OR Inflammation[tiab] OR Metabolism[tiab])

**Abbreviation: mh, mesh; tiab, title/abstract.*

3. RESULTS AND DISCUSSION

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).

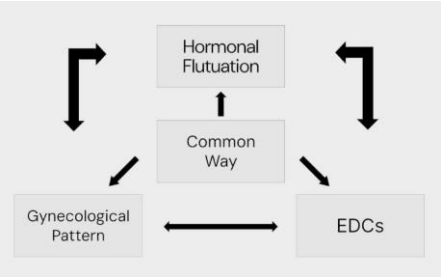

Figure 1 Shows the interconnection (Common Pathway) among hormonal fluctuation, gynecological patterns and endocrinal disruptors (EDCs).

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. As a pathophysiological genetic component, a consistent imbalance between ERα and ERβ is 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. 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).

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). When binding to alpha estradiol receptors with greater affinity and potency than estradiol itself, these compounds trigger cellular signaling pathways that promote inflammation in adipose tissue. Consequently, adopting anti-inflammatory dietary strategies remains the most effective therapeutic approach for lipedema to date.

Compounds such as bisphenol A (BPA) and phthalates disrupt estradiol signaling by mimicking or antagonizing its effects, leading to abnormal fat accumulation and cellular inflammatory responses. This is particularly relevant in lipedema, where affected adipocytes demonstrate heightened sensitivity to estrogenic stimuli, contributing to disproportionate fat deposition (Al-Ghadban et al., 2024; Lee et al., 2013). BPA and certain pesticides also activate aromatase, increasing estradiol production, which is linked to pathologies such as breast and prostate cancers (Lee et al., 2013; Baravalle et al., 2018). Other endocrine disruptors (EDCs), such as phytoestrogens, can inhibit 17β-hydroxysteroid dehydrogenase (17β-HSD), leading to estradiol retention in adipocytes and other sensitive tissues, including the endometrium and uterus.

Additionally, EDCs influence the expression of genes involved in adipocyte differentiation, such as differentiation inhibitor-3 (ID3), thereby promoting adipocyte proliferation and lipid storage. These disruptors also affect adipose tissue remodeling by altering the activity of enzymes like matrix metalloproteinases (MMPs), particularly MMP14, which plays a key role in adipose tissue fibrosis and hypertrophy (Kruglikov et al., 2020).

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Therapeutic approaches for managing lipedema include minimizing exposure to EDCs, combined with dietary modifications, physical exercise, and targeted hormonal therapy.

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.

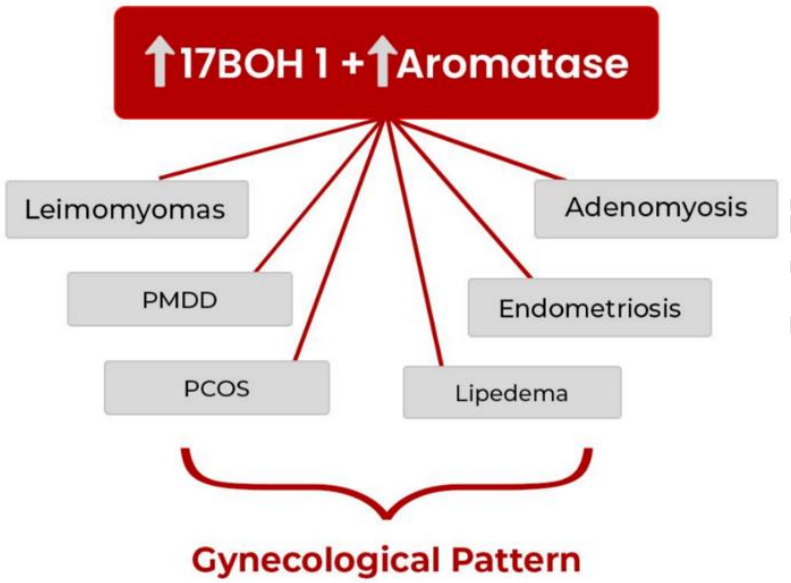

Figure 2. Gynecological pattern and correlation between lipedema and gynecological disorders.
Abbreviation: PMDD, Premenstrual Dysphoric Disorder; PCOS, Polycystic Ovary Syndrome.

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.

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).

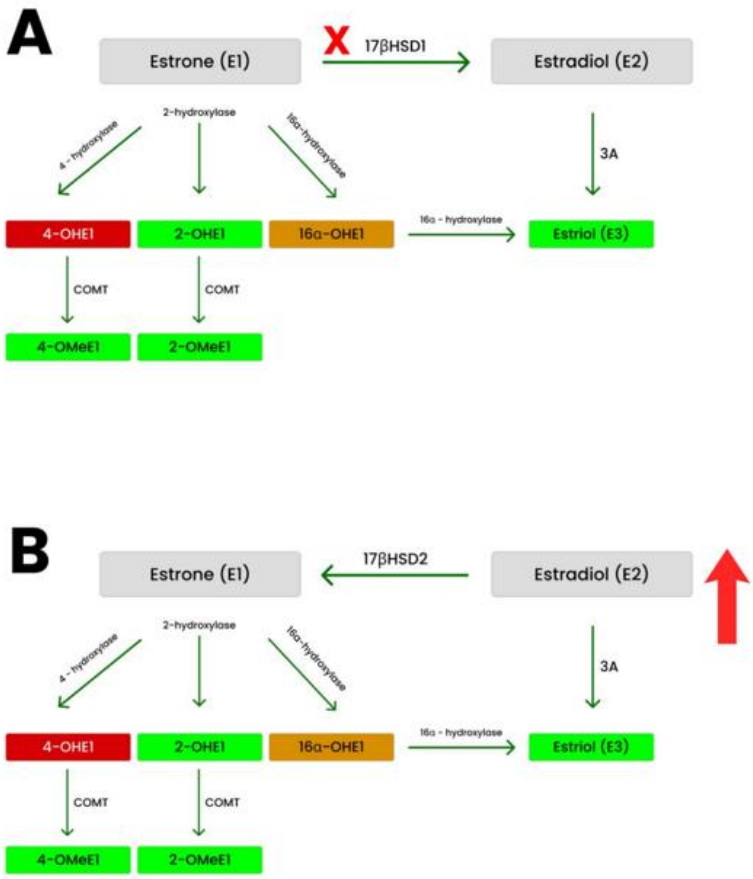

Figure 3 Conversion processes between estrone (E_1) and estradiol (E_2), with dysfunction in the 17β-HSD enzymes.
*Source: Adapted by the authors (*Physicians Lab, 2024).
Abbreviation: COMT, Catecol-O-Metiltransferase; OHE1, hydroxyestrone

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.

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 addressing 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. 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.

For future research, it is recommended to investigate the molecular mechanisms of lipedema using experimental and clinical models, 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.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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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