Does lipoedema mimic pregnancy?

Author: *Samantha Connolly*

In recent years, more attention is being paid to the hormonal aspect of lipoedema. There are suggestions that lipoedema patients may have particular imbalances or sensitivities with regard to oestrogens and/or progesterone. This article examines the specifics of gluteofemoral fat storage during pregnancy: increased gluteofemoral storage with strong resistance to lipolysis. It then asks if hormonal dysregulation in lipoedema patients could result in a hormonal profile that mimics pregnancy. Such a profile may include high levels of oestrogens, progesterone, prolactin and relaxin, or any combination of the above. This pseudopregnancy hormonal profile would instruct the body to store gluteofemoral fat and strongly resist all attempts to mobilise it.

***A Samantha Connolly** is a Neuromuscular Therapist and MLD (Vodder) Therapist (private practice), The Wellness Centre, Main Street, Spiddal, Co. Galway, Ireland*

Lipoedema is a chronic condition characterised by abnormal and painful fat deposition that occurs primarily on the legs, thighs and buttocks, but can also be found in the arms in 80% of cases. The abnormal gynoid adiposity is associated with a body mass index (BMI) that is normal or increased without abdominal adiposity (Paolacci et al, 2018). An estimated 8% to 17% of adult women worldwide are affected and self-reported positive family history of lipoedema has been found for up to 64% of women (Michelini et al, 2020).

Paolacci et al (2018) stated that associated features include: chronic pain that can significantly impact mobility, joint hypermobility and fatigue, bruising due to increased capillary fragility, gait and joint abnormalities, psychosocial stress, anxiety and depression, and oedema in advanced stages. Much research states that a defining trait of lipoedema is that the gynoid and arm fat is highly resistant to diet and exercise, and weight loss may occur only in areas of the body not affected by lipoedema (Herbst, 2012; Al-Ghadban et al, 2019; Michelini et al, 2020). The lead authors of the European Consensus Document (2020) on lipoedema disagree. They reported that patients have achieved substantial weight loss through their clinic's multimodal obesity programme, and that the weight reduction achieved also produces a generally proportional reduction in the circumference of the extremities (Bertsch et al, 2020).

There are two main classifications of lipoedema: the Schingale classification (types I, II, III, IV and V), which is based on the different distribution of adipose tissue (Halk and Damstra, 2017) and the Schmeller and Meier-Vollrath classification (Stages I, II and III), which describes the severity of the disease (Schmeller and Meier-Vollrath, 2008). Men with lipoedema have been reported in the literature only as case reports and tend to have conditions associated with higher oestrogen and lower relative testosterone levels, such as male hypogonadism and liver disease (Torre et al, 2018). Children can also be affected. According to one study, 6.5% of infants with the referral diagnosis of lymphoedema actually suffered from lipoedema (Szél et al, 2014).

Lipoedema must be distinguished from lymphoedema, the cause of which is an impaired lymphatic system. Lipoedema is always bilateral, whereas lymphoedema may be unilateral or bilateral, with possible dominance on one side. Lipoedema also presents with a sharp demarcation

at the ankle, referred to as the "cuff sign" or "reverse shouldering" (Shavit et al, 2018).

In contrast, the feet in lymphoedema are involved in the swelling and the Stemmer sign is positive. Lipoedema starts in the upper legs whereas lymphoedema starts in the lower leg(s) but confusion may arise when lipoedema presents with an additional oedema in the lower legs. Herbst et al (2015) reported that lymphoedema, causing fluid accumulation in the limbs, may develop during any stage of lipoedema, especially stage 3, referred to as lipolymphoedema. Based on the observation of Földi et al (2005) functional and morphological abnormalities of the lymph capillaries are the indicators of impaired lymph formation in lipoedema. Flow in lymphatics in early stages of lipoedema appears normal but can become impeded in later stages accompanied by microaneurysms and leak (Amann-Vesti et al, 2001).

Enlarged lymphatic vessels with beaded appearance were found by MR lymphangiography, which may indicate a subclinical lipolymphoedema state (Lohrmann et al, 2009). Shavit et al (2018) reported that lipoedema is a chronic progressive disease and advanced cases may deteriorate to involve either the lymphatic system (lympholipoedema) or the venous system (venolipoedema) or both.

However, Bertsch et al (2020) argue that the term "lipolymphoedema" is inappropriate because there is no scientific evidence for this viewpoint and say that any lymphoedema associated with lipoedema is obesity-related lymphoedema. They would like to see the term "lipolymphoedema" eliminated from lymphology. Al-Ghadban et al (2019) also state that the fact that most changes found in lymphatic vessel morphology were only in obese lipoedema participants suggests that these individuals may have a greater risk of progressing to lipolymphoedema than non-obese participants.

Female adiposity

The differences in adipose depots of men and women are well documented. Women have greater adipose stores in thighs and buttocks; men are more susceptible to abdominal adiposity. This sex difference in adiposity is present at birth. Female babies have more subcutaneous fat than do male babies for all gestational ages. Pre-pubertal girls have more fat in their legs and pelvis than do pre-pubertal boys (Power and Schulkin, 2007). Oestradiol favours the deposition of subcutaneous fat; lack of oestrogen in women leads both to weight gain and larger proportion of adipose gain in visceral fat (Power and Schulkin, 2007).

Maternal gluteofemoral fat

During pregnancy, the normal female pattern of preferentially storing gluteofemoral fat becomes amplified, with increased fat storage and lipolysis resistance (Rebuffé-Scrive et al, 1985). Butte (2000) reported that changes in lipid metabolism promote the accumulation of fat stores in early and mid-pregnancy and enhance fat mobilisation in late pregnancy. In early pregnancy, increased oestrogen, progesterone and insulin favour lipid deposition and inhibit lipolysis. Lipolysis in response to catelcholamines is markedly higher in the abdominal than the femoral region.

Interestingly, the femoral cells are virtually unresponsive to catecholamines in pregnancy (Butte, 2000). Lassek and Gaulin (2008) postulate that maternal gluteofemoral fat is important for infant neural development, reporting that gluteofemoral fat is the main source of long-chain polyunsaturated fatty acids (LCPUFAs), especially the omega-3 docosahexaenoic acid (DHA), that are critical for foetal and infant brain development. Gluteofemoral fat is richer in essential LCPUFAs than abdominal and visceral fat. Studies using isotope-labelled fatty acids show that 60–80% of LCPUFAs in human breast milk come from maternal fat stores, the mother's gluteofemoral fat, rather than from the mother's current dietary intake (Lassek and Gaulin, 2008).

Prolactin

Levels of another hormone called prolactin also increase during pregnancy. Prolactin is a pituitary hormone, which is most well-known for its role in lactation and suppression of reproduction, but it has other diverse physiological functions, including water and electrolyte balance (Bole-Feysot et al, 1998). "Biochemical hyperprolactinemia" (an excess of prolactin above a reference laboratory's upper limits) can be identified in up to 10% of the population (Serri et al, 2003). Symptoms of hyperprolactinemia primarily include abnormal menstruation patterns but additional findings may include acne, weight gain and increased adiposity (Levine and Muneyyirci-Delale, 2018). To the author's knowledge, this is the first article that asks if prolactin abnormalities could be part of the lipoedema hormonal profile.

Földi and Földi (2005) found that, in their experience, the incidence of lipoedema is increased following head injury or resection of pituitary adenoma. Among pituitary adenomas, prolactin-producing pituitary tumours are the most common type (Serri et al, 2003). The author knows of one patient with lipoedema (type III/IV, stage I) who tested with normal oestrogen and progesterone but extremely

high prolactin levels. The patient underwent hormonal tests following a head injury and prolactin levels were found to be 10 times higher than normal. This patient was ultimately found to have a pituitary tumour (benign) resulting in hyperprolactinemia. However, because the hormonal testing only occurred after the head injury, it is impossible to know if her prolactin levels were already abnormal prior to that (personal communication).

Bano et al (2009) report on a novel association of lipoedema with a Pit-1 gene mutation in a family. A young male was referred to the clinic with diagnosis of idiopathic isolated growth hormone deficiency where a detailed family history revealed short stature and leg swelling, which only affected females in four generations of the family. The proband had growth hormone deficiency, secondary hypothyroidism and hypoprolactinemia. His mother had the Pit-1 mutation (with hypoprolactinemia and growth hormone deficiency) while his phenotypically normal half-sister did not have the mutation. González-Parra et al (1996) reported that changes in circulating levels of sex steroids modulate the expression of Pit-1 in the anterior pituitary and that these changes can be correlated with commensurate modifications in GH (growth hormone) and PRL (prolactin) mRNA levels. Furthermore, the effect on both Pit-1 and PRL mRNA levels occurs, at least in part, at the level of the anterior pituitary and is an oestrogen-receptor-mediated event.

Fat cells from different regions (abdominal, gluteofemoral) show a differential response during pregnancy and lactation. Prolactin may exert an important regulatory effect on the LPL activity in these sites (Rebuffé-Scrive et al, 1985). Prolactin is also produced by adipose tissue and stimulates adipogenesis and inhibits lipolysis; it promotes insulin sensitivity (Levine and Muneyyirci-Delale, 2018). The author was told by one lipoedema patient (type III/IV, stage I) that the only time she had "skinny legs" was while breastfeeding each of her children (personal communication).

Al-Ghadban et al (2019) compared thigh tissue from lipoedema patients (both obese and non-obese) with controls. They found that lipoedema patients have large fat cells (in this area) and that this adipocyte hypertrophy occurs independently of obesity by the usual measure of BMI. Rebuffé-Scrive et al (1985) examined the fat cell metabolism in different regions in women and found that the fat cells in both abdominal and femoral regions were larger in lactating women than controls (including pregnant women). This author was unable to find any study comparing femoral fat cells of lipoedema patients to those of pregnant women but speculates that the results would be informative.

Relaxin

There is some mention of hypermobility as a feature of lipoedema (Herbst et al, 2015; Beltran and Herbst, 2017; Paolacci et al, 2018). Hypermobility presenting in tandem with lipoedema has also been this author's observation. Szél et al (2014) reported that an intrinsic connective tissue defect has been suspected in lipoedema, which may cause musculofacial insufficiency and loss of skin elasticity. If hypermobility and connective tissue laxity are an issue in lipoedema, the hormone relaxin may be implicated.

In humans relaxin exists as three gene products, H1, H2 and H3. Relaxin H2 is the major stored and circulating form of relaxin in humans, and appears to have long-term effects on connective tissues by altering the turnover of collagen and proteoglycans (Kapila, 2003). Relaxin is predominantly associated with a number of pregnancy-related functions involving extracellular matrix (ECM) turnover and collagen degradation. However, relaxin's ability to reduce matrix synthesis and increase matrix degradation has important implications outside of pregnancy.

Relaxin H2 has been demonstrated to successfully reverse collagen accumulation in several organs, such as the skin, lung, liver, kidney and heart of every *in vivo* model of induced fibrosis studied to date (Samuel et al, 2005). For the matrix degradative component of the remodelling cycle, relaxin appears to act primarily by modulating the induction of several matrix metalloproteinases (MMPs) including collagenase and stromelysin (Kapila, 2003).

The MMPs are proteolytic enzymes capable of degrading the ECM and they are balanced by a regulatory component, tissue inhibitors of metalloproteinases (TIMPs). The MMPs and TIMPs act in concert to control the site and extent of ECM turnover throughout the body (Curry and Osteen, 2003). MMPs are known to contribute substantially to tissue degradation in inflammatory joint diseases including rheumatoid arthritis and osteoarthritis (Kapila, 2003). Loss of control of the MMP system leads to extensive and often destructive degradation of the ECM as seen in arthritis and cancer (Curry and Osteen, 2003). The MMP system also controls aspects of reproductive function (Curry and Osteen, 2003).

Writing about the collagen destruction that occurs in cellulite, Mazioti (2018) notes that during menstruation the level of MMPs is high in order for

endometrial bleeding to be achieved. The collagen destruction that they cause is not limited only to the endometrium, but it also concerns the CT and dermis.

Hashem et al (2006) found that β-oestradiol, relaxin, or β-oestradiol+relaxin caused a significant loss of GAGs and collagen from the pubic symphysis and TMJ disc and of collagen from articular cartilage but not from the knee meniscus. Progesterone prevented relaxin- or β-oestradiol-mediated loss of these molecules. They speculated that these hormones may play an important regulatory role in the normal and pathologic metabolism of cartilaginous tissues, by modulating the remodelling of the ECM of cartilage, and that individuals with abnormal absolute or relative levels of one or more of these hormones or their receptors might incur progressive loss of matrix macromolecules, leading to joint disorders characterized by the degeneration of specific cartilages or fibrocartilages.

Various animal and human studies show strong support that the MMP proteolytic cascade associated with ovulation is regulated, in part, by progesterone (Curry and Osteen, 2003). Samuel et al (1996) studied the effects of relaxin on the nonpregnant rat pubic symphysis in conjunction with oestrogen and progesterone. Oestrogen primed rats produced a greater reduction in total collagen content but had no significant effect on collagen solubility or composition when treated with relaxin. This enhanced effect from oestrogen priming was lost when progesterone was added. They concluded that relaxin has potent inhibitory effects on the amount of collagen that is potentiated by oestrogen and antagonised by progesterone. It may be worth noting that PCOS patients have elevated MMP activity (Curry and Osteen, 2003).

Microangiopathy is one of the early histological features of the lipoedema pathomechanism (Szél et al, 2014). Relaxin is able to stimulate the formation of new blood vessels, not only in pregnancy but also in tumorigenesis or ischaemic wounds, through the upregulation of vascular endothelial growth factor (VEGF) transcripts (Feijóo-Bandin et al, 2017).

Collectively, the VEGFs and their receptors are critical regulators of angiogenesis and lymphangiogenesis (Jones and Min, 2011). However, in breast cancer, it has been suggested that VEGF generates leaky, haemorrhagic, immature vessels (Szél et al, 2014). Macrophages in adipose tissue secrete signalling factors, including VEGF, which trigger the formation of leaky lymphatic vessels leading to further swelling, inflammation and obesity (Jones and Min, 2011). Interestingly, a study examining effects of shock-wave therapy in patients with lipoedema or cellulite found nearly fourfold higher plasma mean VEGF levels at baseline compared to non-lipoedematous individuals (Siems et al, 2005).

Relaxin promotes vasodilation through a mechanism that involves NO (nitric oxide) production in a wide range of organs and tissues (Feijóo-Bandin et al, 2017). This can occur in reproductive organs (mammary glands, uterus) but also in subcutaneous fat (McGuane et al, 2011). The mechanisms that regulate relaxin and its receptor expression in the different tissues in which they are produced are not yet known (Feijóo-Bandin et al, 2017). It is also suggested that different concentrations of relaxin can activate its receptor in a different way (Bathgate et al, 2013).

To summarise: the hormone relaxin modulates induction of MMPs (which regulate extracellular matrix synthesis and degradation), and its action is affected by oestrogens and progesterone. An increased presence of relaxin causes up-regulation of VEGF (which leads to angiogenesis). Thus, there are links between relaxin and various lipoedema pathophysiologies (loose connective tissue, microangiopathy and sex steroid involvement).

Lipoedema and female hormones

Some lipoedema studies speculate that there is an association with female hormones and that the disease manifests at times of hormonal turbulence such as puberty, childbirth or menopause (Szél et al, 2014; Al-Ghadban et al, 2019; Buso et al, 2019; Wright and Herbst, 2021). Schmeller and Meier-Vollrath note that the literature emphasises the manifestation of lipoedema during puberty but their own experience shows that onset also frequently occurs after pregnancy (Schmeller and Meier-Vollrath, 2008). However, the European Consensus Document states that there is no evidence that lipoedema starts in puberty (Bertsch et al, 2020).

Oestrogens are well-studied female hormones — and are known to influence wide-ranging areas of health, such as reproductive status, adipose distribution, skeletal stability, immune responses, emotional lability, neural development, cognition and disease susceptibility (Yu et al, 2001; Simpson et al, 2005; Sherwin, 2012; Klein and Flanagan, 2016; Baker et al, 2017; Jenks et al, 2017; Eaton and Sethi, 2019). Oestrogens are known for having an anti-inflammatory effect, but they can also

act in a pro-inflammatory manner, depending on variables such as cell types, timing and concentration of doses (Straub, 2007).

Al-Ghadban et al (2019) reported on findings that suggest that inflammation and angiogenesis may occur independently of obesity in lipoedema. Levels of oestradiol may be a causative factor. Straub (2007) stated that systemic super-systems, such as the hypothalamic-pituitary-adrenal axis, the sensory nervous system and the sympathetic nervous system can be influenced by oestrogens to establish a pro-inflammatory milieu.

Pain is one of the defining features of lipoedema; a lipoedema presentation without pain is classified as lipohypertrophy (Bertsch et al, 2020). Oestrogens are also linked to pain perception. There is evidence that a woman's pain sensitivity increases and decreases throughout her menstrual cycle, with skin, subcutaneous tissue and muscles being affected differently by female hormone fluctuations (Hoffman and Tarzian, 2001).

Fibromyalgia symptoms are associated with the luteal phase, when both oestrogen and progesterone levels are high (Korszun et al, 2000). Pain perception varies according to the menstrual cycle phases in women with chronic pain perception, with patients rating pain significantly higher in some phases of the menstrual cycle than in others (Hellström and Anderberg, 2003). Menopause may also change pain sensitivity. Although the loss of oestrogen can lead to a decrease in life-long painful conditions, such as headache, menopause can also be accompanied by 'new' painful conditions such as osteoporosis and joint inflammation (Meriggiola et al, 2012).

Progesterone is not as well-studied but it is recently being acknowledged as an 'equal player' in women's health homeostasis (Sundström-Poromaa et al, 2020). Interestingly, a recent study has linked lipoedema with a missense variant in a gene that would lead to a slower and less efficient reduction of progesterone to hydroxyprogesterone and an increased subcutaneous fat deposition in variant carriers (Michelini et al, 2020).

Oestrogen receptors must also be considered. Oestrogens bind to and activate their cognate receptors, ERα and ERβ. (Chen and Madak-Erdogan, 2016). Straub (2007) stated that the presence of oestrogen receptors is of outstanding importance because a preponderance of one ER subtype over the other might change oestrogen effects. Reporting on various studies, he concludes that there is suggestion of inflammation-dependent up-regulation of ERβ relative to ERα. It was also demonstrated that hypoxia, which typically accompanies inflammatory conditions, reduced expression of ERα and oxidative stress increased the expression of ERβ (Straub, 2007).

Szél et al (2014) highlighted a study that found decreased ERα and increased ERβ protein level in the gluteal region of overweight-to-obese premenopausal women compared to the level of the abdominal adipose tissue and also observed that the waist-to-hip ratio was inversely related to gluteal ERβ protein and directly related to gluteal ERα/ERβ ratio.

Lipoedema, mental health and hormones

Mental health issues, such as depression or anxiety, are often reported by lipoedema patients. In a 2015 worldwide, internet-supported survey with 1,416 participants, 39.7% women with lipoedema self-reported as having depression (compared with a prevalence of 3–17% in the general population) and 16.5% cited eating disorders (compared with a prevalence of 1–5% in the general population) (Bertsch et al, 2020).

In the European Consensus Document, Bertsch et al (2020) argue that, contrary to the convention that mental disorders arise from lipoedema, the vast majority of women with lipoedema (80%) experience severe psychological symptoms before the onset of lipoedema-related pain and that psychological issues contribute substantially to the development of lipoedema.

This is interesting and relevant because it is well-understood that oestradiol modulates mood and cognition (Douma et al, 2005; Sherwin, 2012; Comasco and Sundström-Poromaa, 2015). Pre-menstrual dysphoric disorder (PMDD) is categorised as a mood disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). It is defined by the onset of functionally impairing or distressing affective, behavioural and physical symptoms in the late luteal phase of ovulatory menstrual cycles.

Converging evidence suggests that progesterone fluctuations are a key factor for causing PMDD and it is thought that women with PMDD have an increased sensitivity to these fluctuations (Sundström-Poromaa et al, 2020). However, oestradiol seems to play a role in regards to PMDD symptoms as progesterone in combination with a high oestrogen dose seems more symptom provoking than progesterone combined with a low oestrogen dose (Segebladh et al, 2009). Given that oestrogen is heavily involved in up-regulating progesterone receptors (in the brain and elsewhere), an increased availability of oestrogen may thus result in a larger number of

progesterone receptors for progesterone to act upon (Sundström-Poromaa et al, 2020).

If mental health disturbances can be linked to both lipoedema and hormonal imbalances, it adds weight to the case for investigation into hormonal imbalance or increased sensitivity to certain hormones as a root cause of lipoedema. A recent study has also made this link. Michelini et al (2020) stated that the correlation between mood disorder and subcutaneous fat deposition suggests the involvement of steroids metabolism and neurohormones signalling, while confirming that no clear association has been established so far. As mentioned earlier, stress is strongly linked to hyperprolactinemia. If lipoedema patients are experiencing mood disturbance as a result of hormonal influence, these bouts of anxiety and depression (and other mental agitations) may conceivably raise stress levels, which could result in hyperprolactinemia. Increased prolactin levels could then act as a root cause, or contributory factor, in the accumulation of gluteofemoral adipose tissue.

Conclusion

The relationship between lipoedema and hormones has not been sufficiently investigated. One reason may be the overwhelming complexity of female hormones. The effects of hormones such as oestrogen, progesterone, relaxin and prolactin can be inhibited or potentiated depending on variables such as (a) the hormone levels or concentrations (b) the presence of other hormones or (c) the distribution of particular receptors. Perhaps due to this complexity, for much of medical history the complication of female hormones has simply been evaded. Until recently, drug trials very often excluded women, largely because it was feared their menstrual cycles could skew results (Bryson, 2019).

Not only have doctors, scientists and researchers mostly been men, but most of the cells, animals and humans studied in medical science have also been male: most of the advances we have seen in medicine have come from the study of male biology (Jackson, 2019). However, a true understanding of lipoedema will be impossible without tackling this complex aspect of the disease. Fortunately, the study of hormones is expanding and there exists much research on oestrogens, progesterone, prolactin and relaxin which could usefully be applied to the study of lipoedema. It is hoped that these observations on the hormonal profiles of women — particularly pregnant women — might provide a jumping off point for the discussion of a possible lipoedema hormonal profile. WINT

References

Al-Ghadban S, Cromer W, Allen M et al (2019) Dilated blood and lymphatic microvessels, angiogenesis, increased macrophages, and adipocyte hypertrophy in lipedema thigh skin and fat tissue. *J Obes* 2019: 8747461

Amann-Vesti BR, Franzeck UK, Bollinger A (2001) Microlymphatic aneurysms in patients with lipedema. *Lymphology* 34(4): 170–5

Baker JM, Al-Nakkash L, Herbst-Kralovetza MM (2017) Estrogen–gut microbiome axis: physiological and clinical implications. *Maturitas* 103: 45–53

Bano G, Mansour S, Brice G et al (2009) Pit-1 mutation and lipoedema in a family. *Exp Clin Endocrinol Diabetes* 118(6): 377–80

Bathgate RD, Halls ML, van der Westhuizen ET et al (2013). Relaxin family peptides and their receptors. *Physiol Rev* 93(1): 405–80

Beltran K, Herbst KL (2017) Differentiating lipedema and Dercum's disease. *Int J Obes (Lond)* 41(2): 240–5

Bertsch T, Erbacher G, Corda D et al (2020) Lipoedema: a paradigm shift and consensus. *J Wound Care* 29(Sup11b): 1–51

Bole-Feysot C, Goffin V, Edery M et al (1998) Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. *Endocr Rev* 19(3): 225–68

Bryson B (2019) *The Body*. London: Penguin Random House

Buso G, Depairon M, Tomson D et al (2019) Lipedema: a call to action! *Obesity (Silver Spring)* 27(10): 1567–76

Butte NF (2000) Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. *Am J Clin Nutr* 71(5 Suppl): 1256S–61S

Chen KL, Madak-Erdogan Z (2016) Estrogen and microbiota crosstalk: should we pay attention? *Trends Endocrinol Metab* 27(11): 752–5

Comasco E, Sundström-Paromaa I (2015) Neuroimaging the menstrual cycle and premenstrual dysphoric disorder. *Curr Psychiatry Rep* 17(10): 77

Curry TE Jr, Osteen KG (2003) The matrix metalloproteinase system: changes, regulation, and impact throughout the ovarian and uterine reproductive cycle. *Endocr Rev* 24(4): 428–65

Douma SL, Husband C, O'Donnell ME et al (2005) Estrogen-related mood disorders: reproductive life cycle factors. *ANS Adv Nurs Sci* 28(4): 364–75

Eaton SA, Sethi JK (2019) Immunometabolic links between estrogen, adipose tissue and female reproductive metabolism. *Biology (Basel)* 8(1): 8

Feijóo-Bandin S, Aragón-Herrara A, Rodríguez-Penas D et al (2017) Relaxin-2 in cardiometabolic diseases: mechanisms of actions and future perspectives. *Front Physiol* 8: 599

Földi E, Földi M (2005) Lipedema. In: Földi E, Földi M, Kubik S (eds.) *Textbook of Lymphology* (in English). Munich, Amsterdam, New York: Elsevier pp418–27

González-Parra S, Chowen JA, García-Segura LM, Argente J (1996) In vivo and in vitro regulation of pituitary transcription factor-1 (Pit-1) by changes in the hormone environment. *Neuroendocrinology* 63(1): 3–15

Halk AB, Damstra RJ (2017) First Dutch guidelines on lipedema using the international classification of functioning, disability and health. *Phlebology* 32(3): 152–9

Hashem G, Zhang Q, Hayami T et al (2006) Relaxin and β-estradiol modulate targeted matrix degradation in specific synovial joint fibrocartilages: progesterone prevents matrix loss. *Arthritis Res Ther* 8(4): R98

Hellström B, Anderberg UM (2003) Pain perception across the menstrual cycle phases in women with chronic pain. *Percept Mot Skills* 96(1): 201–11

Herbst, KL (2012) Rare adipose disorders (RADs) masquerading as obesity. *Acta Pharmacol Sin* 33(2): 155–72

Herbst K, Mirkovskaya L, Bharhagava A et al (2015) Lipedema fat and signs and symptoms of illness, increase with advancing stage. *Arch Med* 7: 1–8

Hoffman DE, Tarzian AJ (2001) The girl who cried pain: a bias against women in the treatment of pain. *J Law Med Ethics* 29(1): 13–27

Jackson G (2019) *The Female Problem: How Male Bias in Medical Trials Ruined Women's Health*. The Guardian (13.11.2019). Available at: https://bit.ly/3KxYe46 (accessed 11.04.2022)

Jenks MZ, Fairfield HE, Johnson EC et al (2017) Sex steroid hormones regulate leptin transcript accumulation and protein secretion in 3T3-L1 cells. *Sci Rep* 7(1): 8232

Jones D, Min W (2011) An overview of lymphatic vessels and their emerging role in cardiovascular disease. *J Cardiovas Dis Res* 2(3): 141–52

Kapila S (2003) Does the relaxin, estrogen and matrix metalloproteinase axis contribute to degradation of TMJ fibrocartilage? *J Musculoskelet Neuronal Interact* 3(4): 401–5

Klein SL, Flanagan KL (2016) Sex differences in immune responses. *Nat Rev Immunol* 16(10): 626–38

Korszun A, Young EA, Engleberg NC et al (2000) Follicular phase hypothalamic-pituitary-gonadal axis function in women with fibromyalgia and chronic fatigue syndrome. *J Rheumatol* 27(6): 1526–30

Lassek WD, Gaulin JC (2008) Waist-hip ratio and cognitive ability: is gluteofemoral fat a privileged store of neurodevelopmental resources? *Evol Human Behav* 29(2008): 26–34

Levine S, Muneyyirci-Delale O (2018) Stress-Induced Hyperprolactinemia: Pathophysiology and Clinical Approach. *Obstet Gynecol Int* 2018: 9253083

Lohrmann C, Földi E, Langer M (2009) MR imaging of the lymphatic system in patients with lipedema and lipo-lymphedema. *Microvasc Res* 77(3): 335–9

Mazioti M (2018) The Potential Role of Endocrine Disrupting Chemicals in Cellulite. *Med Hypotheses* 116: 132–5

McGuane J T, Debrah J E, Sautina L et al (2011). Relaxin induces rapid dilation of rodent small renal and human subcutaneous arteries via PI3 kinase and nitric oxide. *Endocrinology* 152(7): 2786–96

Meriggiola MC, Nanni M, Bachiocco V et al (2012) Menopause affects pain depending on pain type and characteristics. *Menopause* 19(5): 517–23

Michelini S, Chiurazzi P, Marino V et al (2020) Aldo-Keto Reductase 1C1 (AKR1C1) as the First Mutated Gene in a Family with Nonsyndromic Primary Lipedema. *Int J Mol Sci* 21(17): 6264–77

Paolacci S, Precone V, Acquaviva F et al (2019) Genetics of lipedema: new perspectives on genetic research and molecular diagnoses. *Eur Rev Med Pharmacol Sci* 23(13): 5581–94

Power ML, Schulkin J (2007) Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *Br J Nutr* 99(5): 931–40

Rebuffé-Scrive M, Enk L, Crona N et al (1985) Fat cell metabolism in different regions in women. *J Clin Invest* 75(6): 1973–6

Samuel CS, Butkus A, Coghlan JP, Bateman JF (1996) The effect of relaxin on collagen metabolism in the non-pregnant rat pubic symphysis: The influence of estrogen and progesterone in regulating relaxin activity. *Endocrinology* 137(9): 3884–90

Samuel CS, Lekgabe ED, Mookerjee I (2005) The effects of relaxin on extracellular matrix remodeling in health and fibrotic disease. In: Agoulnik AI (eds.) *Relaxin and Related Peptides. Advances in Experimental Medicine and Biology* (AEMB, vol 612). Springer: New York, NY

Schmeller W, Meier-Vollrath I (2008) In: Weissleder and Schuchhardt. *Lymphedema, Diagnosis and Therapy* (4th edn.) Viavital Verlag GmbH: Köln, Germany

Segebladh B, Borgstrom A, Nyberg S et al (2009) Evaluation of different add-back estradiol and progesterone treatments to gonadotropin-releasing hormone agonist treatment in patients with premenstrual dysphoric disorder. *Am J Obstet Gynecol* 201(2): 139. e1-e8

Serri O, Chik CL, Ehud U, Ezzat S (2003) Diagnosis and management of hyperprolactinemia. *CMAJ* 169(6): 575–81

Shavit E, Wollina U, Alavi A (2018) Lipoedema is not lymphoedema: A review of current literature. *Int Wound J* 15(6): 921–8

Sherwin BB (2012) Estrogen and cognitive functioning in women: lessons we have learned. *Behav Neurosci* 126(1): 123–7

Siems W, T Grune, P Voss, et al (2005) Anti-fibrosclerotic effects of shock wave therapy in lipoedema and cellulite. *Biofactors* 24(1–4): 275-82

Simpson ER, Misso M, Hewitt KN et al (2005) Estrogen—the good, the bad, and the unexpected. *Endocr Rev* 26(3): 322–30

Sundström-Poromaa I, Comasco E, Sumner R, Luders E (2020) Progesterone – friend or foe? *Front Neuroendocrinol* 59: 100856

Straub RH (2007) The Complex Role of Estrogens in Inflammation. *Endocr Rev* 28(5): 521–74

Szél E, Kemény L, Groma G, Szolnoky G (2014) Pathophysiological dilemmas of lipedema. *Med Hypotheses* 83(5): 599–606

Torre YS, Wadeea R, Rosas V, Herbst KL (2018) Lipedema: friend and foe. *Horm Mol Biol Clin Investig* 33(1): /j/hmbci.2018.33.issue-1/hmbci-2017-0076/hmbci-2017-0076.xml. doi: 10.1515/hmbci-2017-0076

Wright FW, Herbst KL (2021) A 41-year-old woman with excessive fat of the lower body since puberty with progression to swollen ankles and feet despite caloric restriction, due to lipedema and protein-calorie malnutrition: a case of stage 3 lipedema. *Am J Case Rep* 22: e930306

Yu WD, Panossian V, Hatch JD et al (2001) Combined effects of estrogen and progesterone on the anterior cruciate ligament. *Clin Orthop Relat Res* 383: 268–81