

EVIDENCE BASED STATEMENT

DOMAIN **12**, Statement **02**

TOPIC: “**hormone therapy impact on venous-lymphatic disease.**”

SEARCH TERMS & SOURCES

(hormonal therapy) AND (vein)
(hormonal therapy) AND ((lymphedema) OR (lipedema))

INCLUSION CRITERIA

- Lower limb only
- Systematic Reviews, Meta-Analysis, Reviews, RCT
- Publication < 10 years, only ENG

SEARCH RESULT BEFORE - AFTER SELECTION

248/17 ; 25/6

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Tepper NK, Marchbanks PA, Curtis KM. Superficial venous disease and combined hormonal contraceptives: a systematic review. Contraception. 2016 Sep;94(3):275-9.
2. Cloarec M, Griton P, Blanchemaison P, et al. Hormones et système veineux [Hormones and venous system]. Phlebologie. 1989 Jul-Oct;42(3):409-20.
3. Cohen J. Insuffisance veineuse et contraception orale [Venous insufficiency and oral contraception]. Rev Fr Gynecol Obstet. 1991 Feb 25;86(2 Pt 2):187-9.

EVIDENCE BASED STATEMENT

Domain 12; Statement 2

IDENTIFIED REFERENCES

1. Badreddine J, Lee MH, Mishra K, et al. Continuing perioperative estrogen therapy does not increase venous thromboembolic events in transgender patients: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci.* 2022 Apr;26(7):2511-2517.
2. Bukhari S, Fatima S, Barakat AF, et al. Venous thromboembolism during pregnancy and postpartum period. *Eur J Intern Med.* 2022 Mar;97:8-17.
3. Sobel TH, Shen W. Transdermal estrogen therapy in menopausal women at increased risk for thrombotic events: a scoping review. *Menopause.* 2022 Jan 14;29(4):483-490.
4. Kaemmler LM, Stadler A, Janka H, et al. The impact of micronized progesterone on cardiovascular events - a systematic review. *Climacteric.* 2022 Feb 3:1-10.
5. Teal S, Edelman A. Contraception Selection, Effectiveness, and Adverse Effects: A Review. *JAMA.* 2021 Dec 28;326(24):2507-2518.
6. Morfousse F, Zamora A, Marchaud E, et al. Sex Hormones in Lymphedema. *Cancers (Basel).* 2021 Jan 30;13(3):530.
7. Aksoy H, Karadag AS, Wollina U. Cause and management of lipedema-associated pain. *Dermatol Ther.* 2021 Jan;34(1):e14364.
8. Forner-Cordero I, Forner-Cordero A, Szolnoky G. Update in the management of lipedema. *Int Angiol.* 2021 Aug;40(4):345-357.
9. de Oliveira ALML, Paschôa AF, Marques MA. Venous thromboembolism in women: new challenges for an old disease. *J Vasc Bras.* 2020 Jul 6;19:e20190148.
10. Ayele HT, Brunetti VC, Renoux C, et al. Testosterone replacement therapy and the risk of venous thromboembolism: A systematic review and meta-analysis of randomized controlled trials. *Thromb Res.* 2021 Mar;199:123-131.
11. Klok FA, Barco S. Optimal management of hormonal contraceptives after an episode of venous thromboembolism. *Thromb Res.* 2019 Sep;181 Suppl 1:S1-S5.
12. Buso G, Depairon M, Tomson D, et al. Lipedema: A Call to Action! *Obesity (Silver Spring).* 2019 Oct;27(10):1567-1576.
13. Wollina U. Lipedema-An update. *Dermatol Ther.* 2019 Mar;32(2):e12805.
14. Houghton DE, Alsawas M, Barrioneuvo P, et al. Testosterone therapy and venous thromboembolism: A systematic review and meta-analysis. *Thromb Res.* 2018 Dec;172:94-103.
15. Beyer-Westendorf J, Bauersachs R, Hach-Wunderle V, et al. Sex hormones and venous thromboembolism - from contraception to hormone replacement therapy. *Vasa.* 2018 Oct;47(6):441-450.
16. Gialeraki A, Valsami S, Pittaras T, et al. Oral Contraceptives and HRT Risk of Thrombosis. *Clin Appl Thromb Hemost.* 2018 Mar;24(2):217-225.
17. Tepper NK, Dragoman MV, Gaffield ME, et al. Nonoral combined hormonal contraceptives and thromboembolism: a systematic review. *Contraception.* 2017 Feb;95(2):130-139.
18. Sitruk-Ware R. Hormonal contraception and thrombosis. *Fertil Steril.* 2016 Nov;106(6):1289-1294.
19. Mohammed K, Abu Dabrh AM, Benkhadra K, et al. Oral vs Transdermal Estrogen Therapy and Vascular Events: A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab.* 2015 Nov;100(11):4012-20.
20. Scarabin PY. Hormone therapy and venous thromboembolism among postmenopausal women. *Front Horm Res.* 2014;43:21-32.
21. Szél E, Kemény L, Groma G, et al. Pathophysiological dilemmas of lipedema. *Med Hypotheses.* 2014 Nov;83(5):599-606.
22. Thrombotic risk of contraceptive transdermal patches and the contraceptive vaginal ring. *Prescrire Int.* 2013 Nov;22(143):266, 268-9. PMID: 24427838.
23. Sandset PM. Mechanisms of hormonal therapy related thrombosis. *Thromb Res.* 2013 Jan;131 Suppl 1:S4-7.

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TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 12, Statement 02, TOPIC: “**hormone therapy impact on venous-lymphatic disease.**”

Sex hormones have an effect on both the vein and lymphatic wall and in their venous and lymph content, therefore potentially leading to inflammation, reflux, oedema and thrombosis. Despite the popular belief, strong evidence based data on the real risk of contraception and substitution hormonal therapy on venous and lymphatic disease are still missing according to these authors search.

Two studies suggest increased risk of venous thrombo-embolism in oral contraceptive users who were already affected by chronic venous disease. Nevertheless, several biases limit the value of this conclusion.

[Tepper NK, Marchbanks PA, Curtis KM. Superficial venous disease and combined hormonal contraceptives: a systematic review. Contraception. 2016 Sep;94(3):275-9].

The hormonal role has been pointed out by a recent review showing how venous thromboembolism remains one of the leading causes of maternal mortality, with a pregnancy and postpartum thrombotic incidence that has not decreased over the past two decades.

[Bukhari S, Fatima S, Barakat AF, et al. Venous thromboembolism during pregnancy and postpartum period. Eur J Intern Med. 2022 Mar;97:8-17].

Recent data suggest transdermal hormonal administration can reduce the venous thrombo-embolic risk in menopausal women. Yet, risk/benefit analysis should be always performed carefully for each and every specific case.

***[Sobel TH, Shen W. Transdermal estrogen therapy in menopausal women at increased risk for thrombotic events: a scoping review. Menopause. 2022 Jan 14;29(4):483-490].**

The effect of estrogen on the lymphatic vessel remain unexplored up to our knowledge, yet, in a parallelism with the hormonal role in the arterial and venous system, the same hormones variation could significantly influence edema formation and lymphatic function.

***[Morfoisse F, Zamora A, Marchaud E, et al. Sex Hormones in Lymphedema. Cancers (Basel). 2021 Jan 30;13(3):530].**

In a similar way, preliminary data suggest a hormonal role also in the lipedema pain context, yet without solid data defining the impact of an eventual hormonal therapy on the disease evolution.

Further studies on this clinically impacting topic are encouraged.

***[Aksoy H, Karadag AS, Wollina U. Cause and management of lipedema-associated pain. Dermatol Ther. 2021 Jan;34(1):e14364].**

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STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 12, Statement 02

“oral and injectable hormone use can increase the risk of venous thrombo-embolism. Transdermal administration can reduce the thrombo-embolic risk but more investigations are needed for a final recommendation”

SELECTED REFERENCES

1. **Tepper NK, Marchbanks PA, Curtis KM. Superficial venous disease and combined hormonal contraceptives: a systematic review. Contraception. 2016 Sep;94(3):275-9**
2. **Bukhari S, Fatima S, Barakat AF, et al. Venous thromboembolism during pregnancy and postpartum period. Eur J Intern Med. 2022 Mar;97:8-17**
3. ***Sobel TH, Shen W. Transdermal estrogen therapy in menopausal women at increased risk for thrombotic events: a scoping review. Menopause. 2022 Jan 14;29(4):483-490**
4. ***Morfousse F, Zamora A, Marchaud E, et al. Sex Hormones in Lymphedema. Cancers (Basel). 2021 Jan 30;13(3):530**
5. ***Aksoy H, Karadag AS, Wollina U. Cause and management of lipedema-associated pain. Dermatol Ther. 2021 Jan;34(1):e14364**

identified LITERATURE BIAS

Different drugs and regimens in heterogeneous populations

SUGGESTED NEXT LINES OF RESEARCH

Clinical and lab assessment of different hormonal protocols in homogeneous study populations