Maturitas 137 (2020) 57–62

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Managing thromboembolic risk with menopausal hormone therapy and hormonal contraception in the COVID-19 pandemic: Recommendations from the Spanish Menopause Society, Sociedad Española de Ginecología y Obstetricia and Sociedad Española de Trombosis y Hemostasia

ARTICLE INFO

Keywords:
COVID-19
Venous thromboembolism prophylaxis
Hormone menopause therapy

ABSTRACT

COVID-19 is associated with a systemic inflammatory response with activation of coagulation in symptomatic patients. The possibility of coagulopathies in peri- and postmenopausal women taking estrogen therapies makes it necessary to consider antithrombotic strategies, such as the use of low molecular weight heparins (LMWH) at specific prophylactic or treatment doses for each individual case, depending on the risk factors that each woman presents.

For such reasons, a panel of experts from various Spanish scientific societies has met to develop usage recommendations for managing menopausal women taking menopausal hormone therapy (MHT) or combined hormonal contraception (CHC) during the COVID-19 pandemic.

1. Introduction

COVID-19 is an illness caused by infection with a new coronavirus (SARS-CoV-2) that is associated with a systemic inflammatory response, with activation of coagulation in patients who develop clinical disease. The coronavirus infection favors the appearance of thrombotic events of varying severity in different territories and has the capacity to produce coagulopathies and even disseminated intravascular coagulation (DIC) [1,2]. The possibility of coagulopathies makes it advisable to consider antithrombotic strategies such as the use of low molecular weight heparins (LMWHs) at specific prophylactic or treatment doses depending on the individual case and the added risk factors. It is therefore important to accurately identify risk factors and prescribe the appropriate form of antithrombotic therapy to improve prognosis and reduce the morbidity and mortality related to COVID-19 [3,4].

Hormonal therapy with estrogens increases the risk of thromboembolic disease [5,6]. Therefore, in the present document we provide a simple description of the treatment algorithms for managing peri- and postmenopausal women who have been diagnosed with COVID-19 and are using menopausal hormone therapy (MHT) or combined hormonal contraception (CHC). A panel of experts from various Spanish scientific societies (Spanish Menopause Society, SMS; Sociedad Española de Ginecología y Obstetricia, SEGO; Sociedad Española de Trombosis y Hemostasia, SETH) met in order to draw up a series of evidence-based recommendations. As a result of this meeting, the panel reached consensus to help guide the care of women with COVID-19 using menopausal hormone therapy (MHT) or combined hormonal contraception (CHC).

Although there is very little evidence so far, clinical guidance is reported with Grades of recommendations [7]. All “Expert Opinion” recommendations were reached through constructive discussion, reaching unanimous consensus agreement.

2. Treatment for women using menopausal hormone therapy

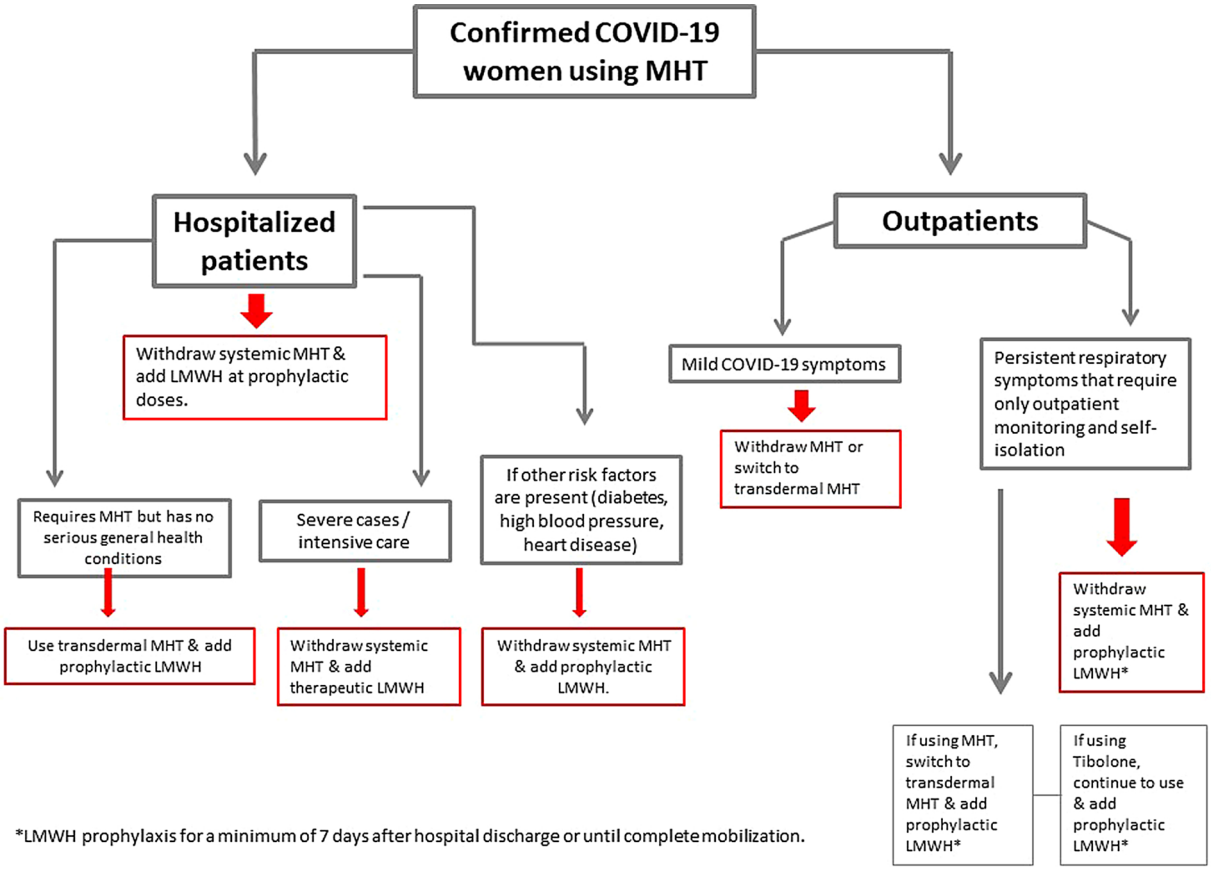
MHT is recommended as the first-line therapy for treating moderate-to-severe menopausal symptoms and for the efficient prevention of long-term estrogen deficiency. This is an estrogen-based therapy that can be administered orally and transdermally. The available evidence on the thromboembolic risks of MHT [8–11] reveals that:

- Transdermal MHT — both estrogenic and combined with progestogen — does not modify the surrogate markers of coagulation and has not been linked to thrombotic risk events in observational studies.
- Tibolone therapy carries a lower risk of thromboembolism than oral MHT.
- Low-dose vaginal estrogens used for genitourinary symptoms are associated with serum estrogen levels that remain well within the postmenopausal range. Moreover, there is no link between these estrogens and an increase in coagulation factors or thromboembolic events.

In addition, recent recommendations suggest that all hospitalized patients with COVID-19 should receive heparin at a prophylactic or therapeutic dose [12], and this could extend after hospitalization, because most episodes of venous thromboembolism occur outside hospital [13].

On the basis of this evidence we recommend:

https://doi.org/10.1016/j.maturitas.2020.04.019
Received 16 April 2020; Received in revised form 25 April 2020; Accepted 29 April 2020

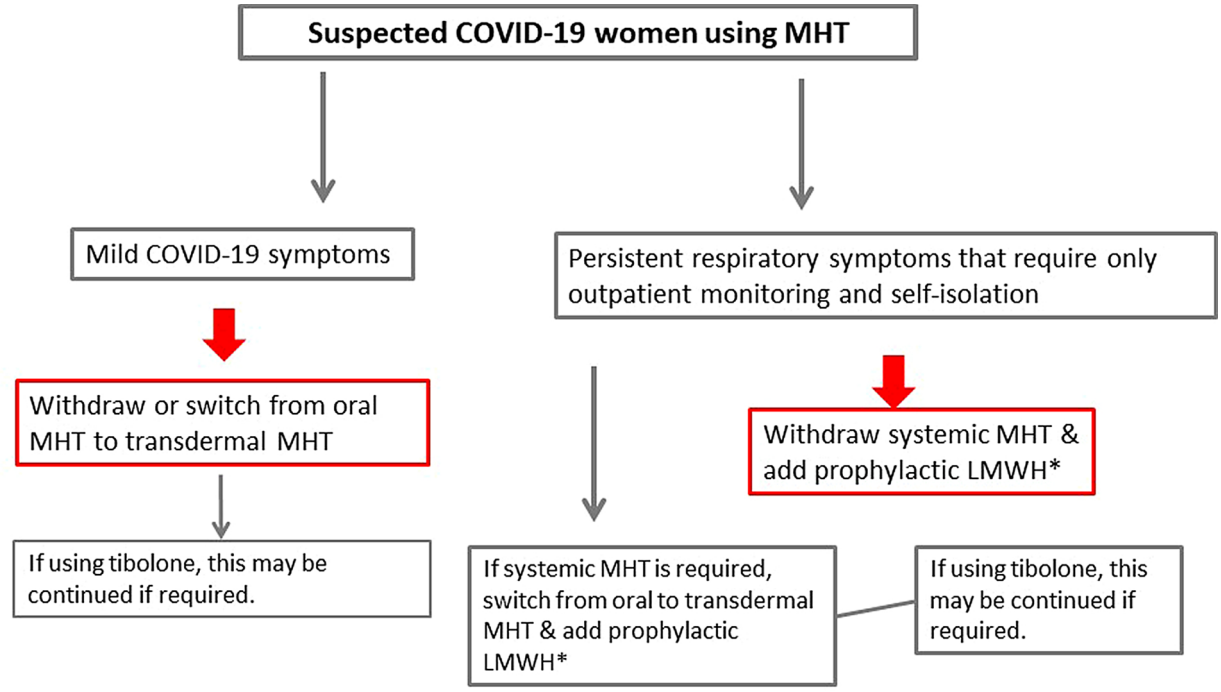


Algorithm 1. Management of confirmed COVID-19 women using MHT.

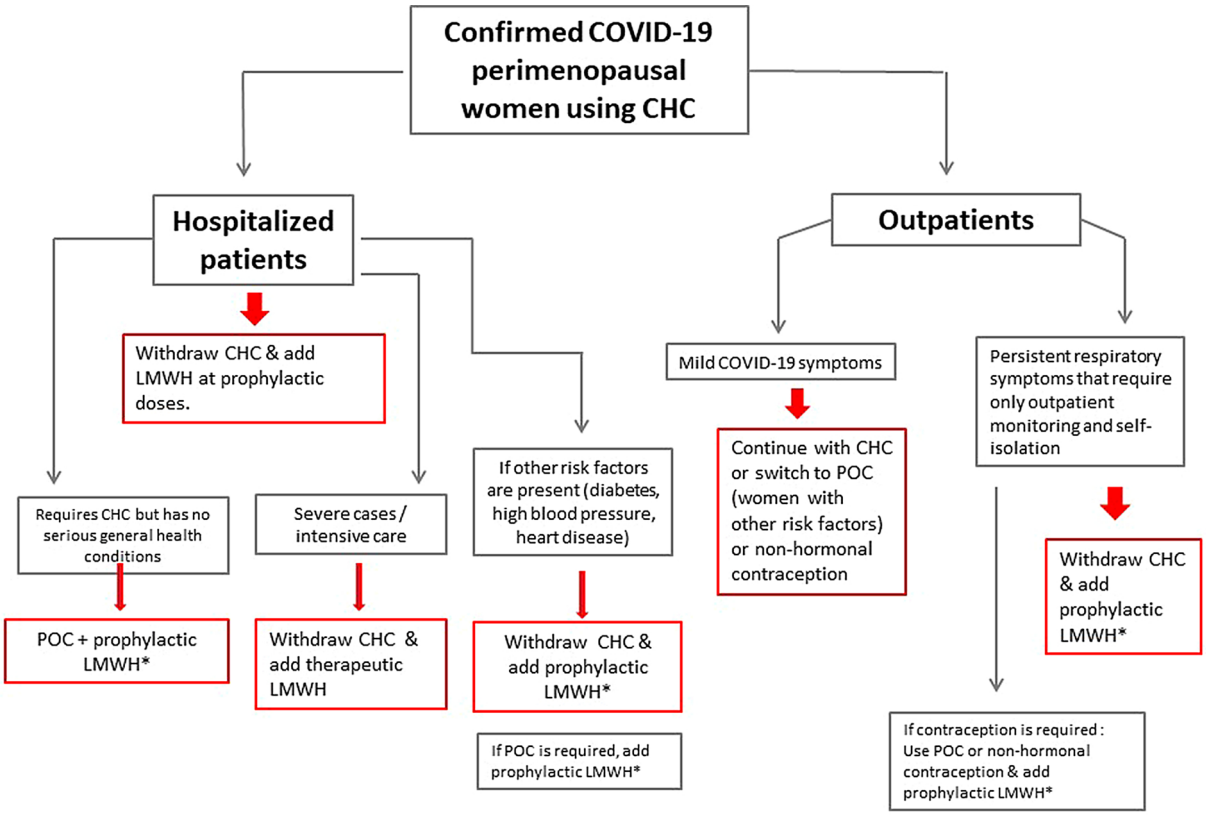
1. For women with confirmed COVID-19 who meet the criteria for hospitalization (see Algorithm 1):
   a. The general recommendation is to withdraw any type of systemic MHT and to immediately administer LMWH at prophylactic doses (Table 1) (Grade C).
   b. When the general condition is not serious and the symptoms require continued treatment with MHT, a change from oral to transdermal therapy may be considered by maintaining LMWH at prophylactic doses (Grade C).
   c. If other risk factors are present (diabetes, high blood pressure or heart disease), it is recommended that MHT is withdrawn and LMWHs are used at prophylactic doses (Grade B).
   d. In severe cases or in women admitted to an intensive care unit (ICU), it is recommended that MHT is withdrawn and LMWHs are administered according to hospital protocol (Grade A).
2. For confirmed COVID-19 patients being treated at home (see Algorithm 1):
   a. If the woman has mild COVID-19 symptoms, it is suggested that MHT is withdrawn during the period of isolation and reduced mobility. In the event that continued treatment with MHT is required, oral MHT may be replaced with transdermal MHT (Grade C).
   b. If the patient has had pneumonia but shows persistent respiratory symptoms, the following actions are recommended:
      i. Withdraw systemic MHT and use LMWH at prophylactic doses (Grade C).
      ii. If menopausal symptomatology is severe and requires treatment with MHT, then it is advisable to switch to transdermal MHT and use LMWH at a prophylactic dose (Grade C). If the patient is receiving tibolone therapy, this may be continued with the use of LMWH at prophylactic doses (Expert Opinion).
      iii. LMWH therapy can be maintained for a minimum of 7 days or until the patient is completely mobilized (Expert Opinion).
3. For symptomatic patients with suspected (but unconfirmed) COVID-19 (see Algorithm 2):

Table 1
Recommended prophylactic heparin dosage in peri and postmenopausal women using menopausal hormone therapy or combined hormonal contraception.

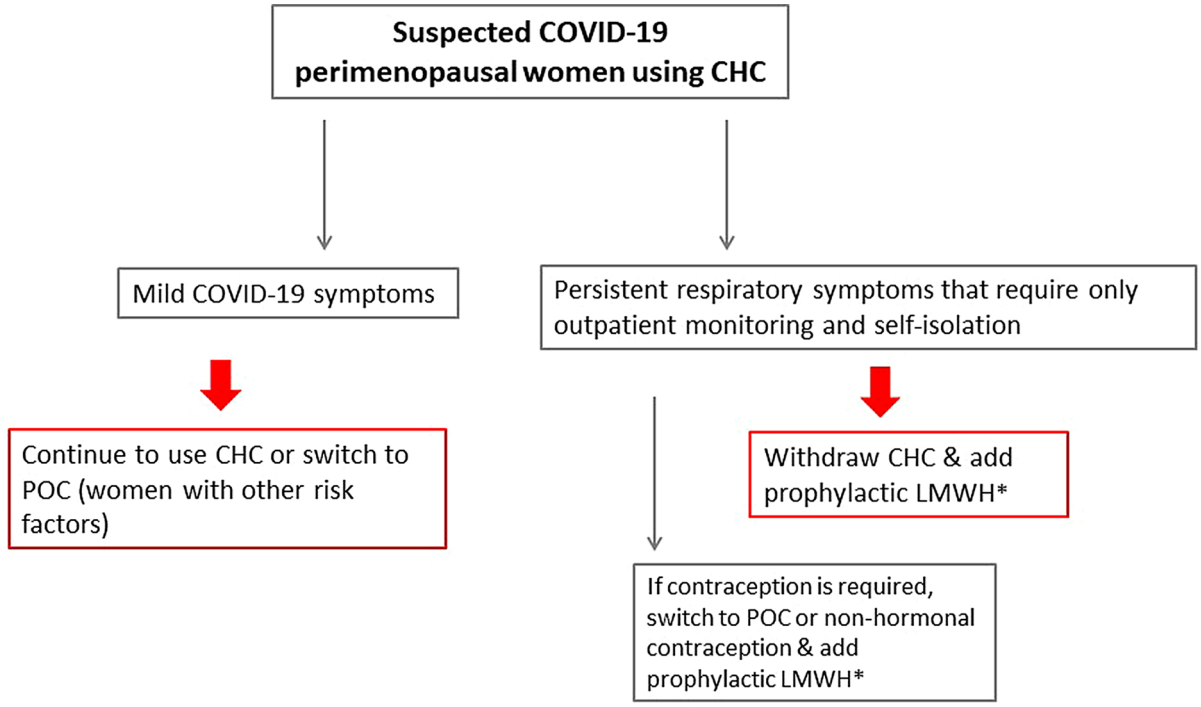
Drug at prophylactic dose	Renal clearance > 30 mL/min	Renal clearance < 30 mL/min
Enoxaparin	• < 80 kg: 40 mg/day (4000 IU/day) • 80–100 kg: 60 mg/day • > 100 kg: 80 mg/day	20 mg/day (2000 IU/day)
Tinzaparin	• < 80 kg: 4500 IU/day (0.45 mL/day) • 80–100 kg: 7000 IU/day • > 100 kg: 10,000 IU/day	Not recommended for use
Bemiparin	• < 80 kg: 3500 IU/day (0.2 mL/day) • 80–100 kg: 5000 IU/day • > 100 kg: 7500 IU/day	2500 IU/day



Algorithm 2. Management of suspected COVID-19 women using MHT.



Algorithm 3. Management of confirmed COVID-19 women using CHC.



Algorithm 4. Management of suspected COVID-19 women using CHC.

a. If the patient has mild symptoms, it is suggested that any form of MHT is withdrawn. If menopausal symptoms require continued use of MHT, it is advised to switch to transdermal MHT. If the woman is receiving tibolone therapy, this may be continued (Expert Opinion).
b. If the patient has had pneumonia but shows persistent respiratory symptoms, the following actions are recommended:
   i. Withdraw systemic MHT and use LMWH at prophylactic doses Grade C).
   ii. If menopausal symptomatology is severe and requires MHT, then it is advisable to switch to transdermal MHT and use LMWH at a prophylactic dose (Grade C). If the patient is receiving tibolone therapy, this may be continued with the use of LMWH at prophylactic doses (Expert Opinion).
   iii. LMWH therapy can be maintained for a minimum of 7 days or until the patient is completely mobilized (Expert Opinion).

3. Treatment for perimenopausal women using hormonal contraception

CHCs are drugs that can be used for contraception or the treatment of gynecological conditions in women up to the time of menopause [14]. Current evidence on the thrombotic risk of CHCs [15–17] suggests that:

- CHCs induce biochemical changes that generate a state of hypercoagulability. Whilst this effect depends on the dose of estrogen, it is modulated by progestogens. The risk of this effect is greater during the first year of use.
- There is a synergistic effect between other risk factors and CHCs in relation to increased thromboembolic risk.
- Progestogen-only contraception (POC) — including progestin-containing IUDs and implants — does not increase the risk of thrombosis; therefore, in situations of transient risk without other additional risks, LMWH prophylaxis will not be needed for the use of POC.

Based on this evidence, it is recommended that:

1. For confirmed COVID-19 patients admitted to hospital (see Algorithm 3):
   a. The general advice is to discontinue any form of treatment with CHCs and immediately administer LMWH at prophylactic doses (Table 1) (Grade C).
   b. If the condition is not serious or CHCs are required for reasons other than contraception (e.g., heavy menstrual bleeding or other indications), the treatment should be switched to progestogen-only contraceptives (POCs), adding LMWH at prophylactic doses (Expert Opinion).
   c. If other risk factors are present (diabetes, high blood pressure or heart disease), it is recommended that the CHCs are withdrawn and LMWHs are used prophylactically (Grade C). Women using POCs may continue this treatment along with LMWHs at prophylactic doses (Expert Opinion).
   d. In severe cases or for women admitted to intensive care, it is recommended that the CHC is withdrawn and LMWH treatment is administered according to hospital protocol (Grade A).
2. For COVID-19 patients being treated at home (see Algorithm 3):
   a. In women with mild symptoms, it is suggested that the CHCs are withdrawn during the period of isolation and reduced mobility. If hormonal contraception is required, it is recommended that treatment with CHC is continued or, alternatively, POC can be used if there is another risk factor. POCs can be used along with LMWHs at prophylactic doses (Expert Opinion).
   b. In women who have had pneumonia but continue to show persistent respiratory symptoms that require only outpatient monitoring and self-isolation, the following actions are recommended:

i. Discontinue CHCs and use prophylactic doses of LMWH (Grade C).
ii. If hormonal contraception cannot be discontinued, it is advisable to switch to POC and add LMWH at a prophylactic dose (Expert Opinion).
iii. LMWH therapy can be maintained for a minimum of 7 days or until the patient is completely mobilized. POCs can be used along with LMWHs at prophylactic doses (Expert Opinion).

3. For symptomatic patients with suspected (but unconfirmed) COVID-19 (see Algorithm 4):
   a. If the woman has mild symptoms and requires hormonal contraception, it is recommended that treatment with CHCs is continued, or, alternatively, POC can be used if there is another risk factor (Grade B).
   b. If the patient has had pneumonia but shows persistent respiratory symptoms that require only outpatient monitoring and self-isolation, the following actions are recommended:
      i. Discontinue CHCs and use LMWH at prophylactic doses (Grade C).
      ii. If hormonal contraception is required, it is advisable to switch to POC with the use of LMWH at prophylactic doses (Expert Opinion).
      iii. LMWH therapy can be maintained for a minimum of 7 days or until the patient is completely mobilized (Expert Opinion).

General recommendations

COVID-19 is likely to remain a problem for many months. Women not using estrogen-based hormonal therapies (MHT or CHC) who are without COVID-19 symptoms should take the preventive and safety measures recommended for the general population. For dealing with patients who have questions regarding MHT or CHC, telephone/video consultation and triage are preferable, with face-to-face visits carried out only if absolutely necessary. It is also essential that women are given an effective form of alternative contraception in order to avoid an unplanned pregnancy and its attendant risks.

In women for whom hormonal therapy has been withdrawn or modified, it is recommended that their pre-COVID treatment is reinstated only after recovery or restoration of full mobility.

The thromboembolic risk in COVID-19 women under hormonal treatment group

Laura Baquedano, Mª Jesús Cancelo, Antonio Cano, Pluvio Coronado, Esther De la Viuda, Plácido Llaneza, Nicolás Mendoza, Borja Otero, Jose Antonio Páramo, Isabel Ramírez, Sonia Sánchez.

Contributors

Isabel Ramírez contributed to conception and design of the idea, and preparation of manuscript.

Nicolás Mendoza contributed to conception and design of the idea, and preparation of manuscript.

Antonio Cano contributed to preparation of manuscript.

All authors participated in data interpretation, and approved the final version of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No external funding was received for the preparation of this article.

Provenance and peer review

This article has undergone peer review.

Acknowledgements

This article has been translated and edited by Your English Lab.

Isabel Ramírez[a], Esther De la Viuda[a,b], Laura Baquedano[a,b], Pluvio Coronado[a,b], Plácido Llaneza[a,b], Nicolás Mendoza[a,b,*], Borja Otero[a,b], Sonia Sánchez[a,b], Mª Jesús Cancelo[a,b], José Antonio Páramo[c], Antonio Cano[a,b],

[a] *Spanish Menopause Society (Asociación Española para el Estudio de la Menopausia — AEEM), Spain*

[b] *Sociedad Española de Ginecología y Obstetricia (SEGO), Spain*

[c] *Sociedad Española de Trombosis y Hemostasia (SETH), Spain*

E-mail addresses: isaramirezp@telefonica.net (I. Ramírez), esterdelaviuda@gmail.com (E. De la Viuda), lbaquedanome@hotmail.com (L. Baquedano), pcoronadom@gmail.com (P. Coronado), pllanezac@hotmail.com (P. Llaneza), nicomendozaladron@gmail.com (N. Mendoza), borja.otero@gmail.com (B. Otero), ssanmen@gmail.com (S. Sánchez), mcanceloh@sego.es (M.J. Cancelo), japaramo@unav.es (J.A. Páramo), Antonio.Cano@uv.es (A. Cano).

References

[1] J. Wang, N. Hajizadeh, E.E. Moore, R.C. McIntyre, P.K. Moore, L.A. Veress, M.B. Yaffe, H.B. Moore, C.D. Barrett, Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series, J. Thromb. Haemost. (April) (2020), https://doi.org/10.1111/jth.14828 [Epub ahead of print].

[2] E. Driggin, M.V. Madhavan, B. Bikdeli, T. Chuich, J. Laracy, G. Bondi-Zoccai, T.S. Brown, C. Nigoghossian, D.A. Zidar, J. Haythe, D. Brodie, J.A. Beckman, A.J. Kirtane, G.W. Stone, H.M. Krumholz, S.A. Parikh, Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic, J. Am. Coll. Cardiol. (March) (2020), https://doi.org/10.1016/j.jacc.2020.03.031 [Epub ahead of print] pii: S0735-1097(20)34637-4.

[3] N. Tang, H. Bai, X. Chen, J. Gong, D. Li, Z. Sun, Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy, J. Thromb. Haemost. (March) (2020), https://doi.org/10.1111/jth.14817 [Epub ahead of print].

[4] FSRH CEU clinical advice to support provision of effective contraception during the COVID-19 outbreak 20 March 2020 file:///C:/Users/Admin/Downloads/fsrh-clinical-advice-to-support-provision-of-effective-contraception-covid-26.3.2020.pdf.

[5] F. Martínez, I. Ramírez, E. Pérez-Campos, K. Latorre, I. Lete, Venous and pulmonary thromboembolism and combined hormonal contraceptives. Systematic review and meta-analysis, Eur. J. Contracept. Reprod. Health Care 17 (2012) 7–29.

[6] Y. Vinogradova, C. Coupland, J. Hippisley-Cox, Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases, BMJ 364 (2019) k4810.

[7] P.G. Shekelle, S.H. Woolf, M. Eccles, J. Grimshaw, Developing clinical guidelines, West. J. Med. 170 (1999) 348–351.

[8] D. Lekovic, P. Miljic, A. Dmitrovic, J. Thachil, How do you decide on hormone replacement therapy in women with risk, Blood Rev. 31 (2017) 151–157.

[9] Beral V. Sweetland, A. Balkwill, B. Liu, V.S. Benson, M. Canonico, J. Green, G.K. Reeves, Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study of venous thromboembolism? J. Thromb. Haemost. 10 (2012) 2277–2286.

[10] N. Mendoza, P. Abad, F. Baró, M.J. Cancelo, P. Llaneza, M. Manubens, F. Quereda, R. Sánchez-Borrego, Spanish Menopause Society position statement: use of tibolone in postmenopausal women, Menopause 20 (July (7)) (2013) 754–760.

[11] K. Mohammed, A.M. Abu Dabrh, K. Benkhadra, A. Al Nofal, B.G. Carranza Leon, L.J. Prokop, V.M. Montori, S.S. Faubion, M.H. Murad, Oral vs transdermal estrogen therapy and vascular events: a systematic review and meta-analysis, J. Clin. Endocrinol. Metab. 100 (November (11)) (2015) 4012–4020, https://doi.org/10.

* Corresponding author at: Maestro Montero, 21, 18004 Granada, Spain.

1210/jc.2015-2237.
[12] J. Thachil, N. Tang, S. Gando, A. Falanga, M. Cattaneo, M. Levi, et al., ISTH Interim Guidance on Recognition and Management of Coagulopathy in COVID-19, [Published: 25 March 2020] (https://clotconnect.wpcomstaging.com/2020/03/26/covid-19-and-coagulopathy-twomanagement-guidance-documents-for-health-care-professionals/) (2020), https://doi.org/10.1111/jth.14810.
[13] J.E. Dalen, P.D. Stein, J.L. Plitt, N. Jaswal, J.S. Alpert, Extended thromboprophylaxis for medical patients, Am. J. Med. 133 (January (1)) (2020) 9–11.
[14] N. Mendoza, R. Sanchez-Borrego, Classical and newly recognised non-contraceptive benefits of combined hormonal contraceptive use in women over 40, Maturitas 78 (May (1)) (2014) 45–50.
[15] S. Mantha, Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis, BMJ 345 (2012) e4944.
[16] Ø. Lidegaard, Thrombotic stroke and myocardial infarction with hormonal contraception, N. Engl. J. Med. 366 (June (24)) (2012) 2257–2266.
[17] M. Bastos, Combined oral contraceptives: venous thrombosis, Cochrane Database Syst. Rev. (March (3)) (2014) CD010813.