Thrombosis & Haemostasis: Research

Open Access

Austin Publishing Group

Review Article

SARS Covid-19 as an Immunothrombotic Disease and the Potential Benefits of a New Estrogen-Free Contraceptive Containing Drospirenone

Regidor PA[1]* and Colli E[2]

[1]Exeltis Europe, Ismaning, Germany

[2]Exeltis HealthCare Madrid, C/ Manuel Pombo Angulo 28, Spain

***Corresponding author:** Pedro-Antonio Regidor, Exeltis Europe, Ismaning, Adalperostr. 84 85737 Ismaning Germany

Received: December 07, 2020; **Accepted:** December 28, 2020; **Published:** January 04, 2021

Abstract

Newly research associate the severity of Covid-19 with obesity and the rise in prothrombotic markers like D-Dimers. As Covid-19 is considered an immunothrombotic disease, the potential benefits of estrogen-free contraceptives like drospirenone are discussed.

Adding estrogens in contraception may rise the cardiovascular risk in Covid-19 and Long Covid patients.

Introduction

SARS-CoV-2 is a member of the family of viruses called Coronaviridae, which includes the virus strains SARS-CoV and Mers-CoV and is characterized by a positive-sense single-stranded RNA genome and a protein coat with protruding glycoproteins (peplomeres) that cause the distinctive corona-like appearance when imaged by electron microscopy [1,2]. Infections with SARS-Cov-2 may lead to systemic inflammatory responses associated with the activation of multiple coagulation processes [3]. Although they are part of the standard host defense mechanisms, they may result in Disseminated Intravascular Coagulation (DIC) and, consequently, critical illness [4,5].

Specific components of microorganisms can bind to pattern-recognizing receptors of immune cells, thereby stimulating the expression of gene products like, for example, Tissue Factor (TF) produced by cells of the monocyte-macrophage lineage [6-8]. The usual inflammatory response of the host also leads to the synthesis of various further pro-inflammatory cytokines with pleiotropic effects, including the initiation of coagulation processes that may result in massive coagulopathy if not appropriately controlled. In order to describe and quantify the degree of coagulation, diagnostic criteria for overt DIC and a Sepsis-Induced Coagulopathy (SIC) score have been developed and validated by the ISTH (International Society of Thrombosis and Haemostasis) [9-11]. SIC is characterized by pronounced changes in coagulation that may continuously progress towards the more severe DIC disease pattern if the primary etiology of sepsis is not rectified [10-12].

Infections with pathogens like viruses, bacteria, or fungi may lead to complex reactions of the innate immune system, finally resulting in so-called immune-thrombosis or thrombo-inflammation. The term describes a pathologic process that is characterized by subsequent activation of coagulation and thrombin generation in response to an inflammatory trigger and, vice versa, the promotion of inflammatory processes by thrombotic events. Both processes are intertwined by a variety of molecular signaling pathways between the components of both systems [13-15].

The progression from normal hemostatic processes to excessive coagulation that finally leads to DIC and may result in multiorgan failure is a subject of intense research. Several procoagulant pathways are activated during inflammation. Polyphosphate groups of microbial origin may activate platelets, mast cells, and Factor XII (FXII), an essential component of the coagulatory response [16,17]. The complement system of the immune system is additionally involved in the activation of coagulation. Furthermore, neutrophils stimulated by microbes or pro-inflammatory compounds release nuclear material (DNA, histones, and other constituents), which forms so-called Neutrophil Extracellular Traps (NETs) that play a role in anti-microbial defense, but may also activate pro-thrombotic pathways leading to thrombin formation [8,18]. Hence, molecular mechanisms triggered by pathogens represent essential factors in the complex interactions between immune response and thrombotic processes in sepsis [8,19]. Additionally, activation of vascular endothelial cells by injury and specific inflammatory cytokines also leads to pro-thrombotic changes [8,20].

Infection with SARS-CoV2 may lead to significant inflammatory responses as measured by an increase in IL-6, C-reactive protein, fibrinogen, and erythrocyte sedimentation rate [21]. Since the virus primarily attaches to ACE2 receptors, activation and damage of affected endothelial cells may lead to the above-described pro-thrombotic changes. Accordingly, enhanced plasma concentrations of pro-inflammatory cytokines have been found in Covid-19 patients with the need for intensive care compared to non-ICU patients in early reports of COVID-19 patients [22]. These inflammatory conditions may lead to subsequent activation of the coagulation response as measured by increased D-Dimers levels, a characteristic parameter for pro-coagulatory conditions. Elevated D-Dimers concentrations have been linked to increased mortality of Covid-19 patients, and both septic patients and those developing DIC conditions are at a higher risk for a fatal course of the disease. Although the mechanisms leading to coagulation during SARS-CoV-2 infection have not been elucidated yet, they instead seem to relate to the host's inflammatory response instead of distinct viral pathogenic factors. In contrast to RNA-stranded viruses associated with hemorrhagic fever like Ebola,

Citation: Regidor PA and Colli E. SARS Covid-19 as an Immunothrombotic Disease and the Potential Benefits of a New Estrogen-Free Contraceptive Containing Drospirenone. Thromb Haemost Res. 2021; 5(1): 1052.

Table 1: Summary of coagulation findings. Adapted from Connors and Levy [24].

1. Coagulopathy is represented by elevated levels of fibrinogen and D-dimers, and minimal changes in PT, aPTT, and platelet count during early infection
2. Dysregulated platelets and neutrophils cooperate to drive a systemic prothrombotic state in SARS-CoV-2 infection, indicating inflammation as trigger for thrombotic complications frequently observed during COVID-19.
3. Microvascular thrombi containing neutrophils, platelets, and Neutrophil Extracellular Traps (NETs) are a hallmark of severe SARS-CoV-2 infection, linking multi-organ failure and systemic hypercoagulability in COVID-19
4. Elevated levels of IL-6 are associated with growing fibrinogen levels
5. An increased concentration of D-dimers at admission is associated with a higher risk for a fatal course of the disease
6. After admission, increasing D-dimer levels indicate growing risk for multiorgan failure and overt DIC. Increase observed in non-survivors at day 4 after admission in non survivors Increase is linked to longer hospitalization and higher risk for sepsis
7. excessive ? bleeding is not associated with Covid-19 disease.

infections with SARS-CoV-2 do not result in excessive bleeding [3]. Data from Wuhan support the view that Covid-19- related coagulopathy instead results from the inflammatory host response that leads to exaggerated thrombotic processes through the above-described thrombo-inflammatory interrelations of different host signaling pathways.

Activated neutrophils and immunogenic platelets generate organ damage and a systemic thrombogenic phase in patients with SARS Covid-19. Recent data of Nicolai et al. [23] define Covid-19 as a dysregulated immunothrombosis.

Moreover, they reported peripheral blood coagulation tests and histopathological signs of microvascular thrombosis in affected organs, which reflects that plasmatic coagulation is distorted towards a procoagulant state correlating with disease severity. They exposed that platelets, neutrophils, and the coagulation cascade determine the ? gravity of the illness, and therefore these elements might be useful pharmacological targets in Covid-19. Additionally, prophylactic anticoagulation and accurate monitoring for thrombotic complications are an essential duty in treating Covid-19 patients.

Table 1 shows the immunothrombotic evidence of Covid-19 [24].

Another recent aspect discussed during Covid-19 is the role of transferrin. Tang et al. [25] identified that transferrin (average plasma concentration ~40μM), fibrinogen, thrombin, factor XIIa (FXIIa), and AT reacts with specific chemical affinity to balance the coagulation pathway. Generally, transferrin is bound with fibrinogen (average plasma concentration ~10μM) at a molar ratio of 4:1. Unusually upregulated transferrin reacts with and stimulates Thrombin/FXIIa and holds up AT's inactivation response on coagulation proteases by binding to AT; hence hypercoagulability is induced.

And this phenomenon has been described by McLaughlin et al. [26], showing that the procoagulant transferrin was upregulated expressed in SARS-CoV-2 infected cells, elevated with age and more common in males than in females. Furthermore, increased transferrin values were detected in individuals during COVID-19 infection. Transferrin is a glycoprotein which carries and distributes iron into the cells via transferrin receptor binding and posterior receptor-mediated endocytosis [27,28]. However, it also stimulates iron-independent coagulation mechanisms as an antithrombin inhibitor, which meddles with the pro-thrombotic activity of coagulation proteases such as thrombin and factor XIIa [25].

Transferrin is primarily produced in the liver. However, (SARS-CoV-2-induced) locally made transferrin may contribute to COVID-19 pathology, even independent of circulating transferrin levels [27-29].

This is an additional element showing the high thrombogenic situation in patients with SARS Covid-19.

Tang [30] also found that transferrin levels are elevated by estrogen administration, suggesting an association between transferrin-upregulation, iron deficiency anemia, and the use of oral contraceptives. Exogenous transferrin, iron deficiency, estrogen administration, or transferrin overexpression like in SARS Covid-19 patients promoted hypercoagulability. They concluded that factors like estrogens upregulating transferrin are risk factors of thromboembolic diseases.

Contraception in Covid-19 times

Combined Hormonal Contraceptives (CHC) are commonly prescribed, broadly tolerated, guarantee adequate contraception, their side effect profile is low, and they even provide supplementary health benefits. The most critical preoccupations regarding their usage are cardiovascular risks- in particular, the Venous Thromboembolism (VTE) risk - which, on the one hand, make impossible the treatment for women with risk factors, and on the other hand, provoke reticence in healthy women [30,31].

In addition to the above-mentioned restriction, the elevated risk of VTE outcomes in healthy COC users is 6-12/10,000 women/year compared to a risk of 2/10,000 women/year in non-users. In the posterior subdivision, in accordance with the latest data of EMA, the risks of the combined preparations with levonorgestrel or norethisterone are 5-7 cases/10,000 women/year, 8-11 cases in the ethinylestradiol-dienogest-containing, and 9-12 cases in the combined formulations with the progestogenic desogestrel, gestodene and drospirenone [32].

As defined by laboratory data, ethinylestradiol has a pro-coagulator effect due to its hepatic metabolism by increasing the factors which are involved in clotting and reducing fibrinolytic factors. Estradiol or estradiol valerate has a lower impact on the liver than ethinylestradiol [33] because of their shorter half-life and faster metabolization. Estrogens modify the hemostasis dynamic balance through an increment of the coagulatory factors (e.g., factor VII) and anti-fibrinolytic factors (e.g., PAI-1). Progressively the number of D-dimers is elevated due to the higher amount of fibrin and its waste compounds in blood. This balance is influenced by the concentration of ethinylestradiol that triggers the coagulation and the sort and dose of progestogen that facilitates anti-fibrinolytic factors such as PAI-1

Table 2: Thromboembolic events and changes from baseline in blood pressure and body weight in the European studies' patient populations [36].

			SBP < 130/DBP<85 (mmHG)	SBP >= 130/DBP >= 85 (mmHG)		BMI < 30kg/m²	BMI >= 30 kg/m²		Thromb embolic events
EU Study 1		Changes from baseline	N = 548			N = 644	N = 41	Total amount of patients	N = 713
	SBP (mmHg)	Mean (SD)	1.77 (10.08)	- 7.59 (9.19)	Mean (SD)	0.14 (1.22)	- 0.77 (3.00)		
		Median	0.0	- 8.0	Median	0	- 0.4	Cases	N = 0
	DBP (mmHg)	Mean (SD)	1.06 (8.20)	- 4.85 (7.85)	Range	- 4.5 to 6.7	- 8.4 to 8.6		
		Median	0.0	- 5.0					
EU Study 2		Changes from baseline	N = 723	N = 130		N = 823	N = 30	Total amount of patients	N = 823
	SBP (mmHg)	Mean (SD)	- 0.3 (10.)	- 8.3 (8.6)	Mean (SD)	0.04 (1.11)	-0.07 (2.41)		
		Median	0.0	- 7.0	Median	0	0	Cases	N = 0
	DBP (mmHg)	Mean (SD)	- 0.8 (7.7)	- 7.2 (8.4)	Range	-5.0 to 5.2	- 8.9 to 4.8		
		Median	0.0	- 5.5					

[34].

In accordance with the results obtained by epidemiological studies, COC elevates the risk of VTE by two to four times, depending on the dose of estrogen and the type of progestogen [31,32]. The rate of thrombotic outcomes is not increased by progestogens per se, aside from those with a partial glucocorticoid activity [34,35].

A novel estrogen-free drospirenone, only oral contraceptive (DRSP POP), has entered the US-American and European market in 2019 and 2020, respectively. The high contraceptive efficacy and excellent safety profile of the 4mg DRSP-POP, even in higher-risk women, have been proven in clinical studies (Table 2) [36,37].

Thromboembolic outcomes

During the clinical development procedure (>20,000 cycles), no VTE outcomes were reported for 4mg drospirenone. Simultaneously no events of arterial thromboembolism, myocardial infarction, stroke, or pulmonary embolism were detected. It is essential to emphasize that a considerable number of participants in phase III clinical trials had risk factors for VTE. History of thromboembolic illness, confirmation of predisposing conditions for vascular or metabolic disease, current smoker >35 years or non-smoker >40 years, and body mass index (BMI) >30 kg/m2 were the documented risk factors. In the USA, at least 367 participants (36.5%) had a risk factor for VTE, while in the European studies, 139 (16.2%) and 104 (14.6%) participants, respectively, had a VTE risk factor [36].

These data were in accordance with a laboratory study conducted in a subgroup of these women.

During an open comparative study with the DRSP-POP and a 75µg – desogestrel-only pill (DSG-POP), the influence of both preparations on hemostatic parameters were evaluated. In this trial, 39 women received the novel 4mg DRSP-POP in a 24+4 regimen (each 24 DRSP tablets followed by four placebo tablets), while 29 participants obtained 75µg DSG daily for nine complete cycles. After completion of the cycles, the hemostatic parameters, including Apc resistance, Antithrombin III, Protein C reactivity, Factor VII, Factor VIII, and D-Dimer, were measured and compared to the baseline level at the begin of the trial (Table 3).

Mean (SD) values of clotting factor VII at baseline was lower in the DRSP group (1.123 (0.2486 SD)) than in the group receiving desogestrel (1.241 (0.2607 SD)) but were comparable at the endpoint. Hence, the change from baseline to endpoint was statistically significant more substantial in the DRSP group compared to the DSG group (p = 0.0088, 2-sample t-test).

At baseline also the mean activity of protein C was lower in the DRSP group than in the DSG group [1.140 (0.2052 SD) versus 1.293 (0.2447 SD); p = 0.0069, 2-sample t test] and changes were identical at endpoint [1.108 (0.1688 SD) for DRSP versus 1.136 (0.2230 SD) for DSG], leading to a significant difference of- 0.0332 in the DRSP versus - 0.157 in the DSG group (p =0.0249, 2-sample t test) in protein C activity.

Hence, the observed differences between FVII and Protein C activity during the trial resulted from differences in the baseline levels.

Furthermore, in the DRSP group, a pronounced reduction of D-Dimer was observed, dropping from baseline values of 264.9 ng/ mL to 215.0 ng/mL at the endpoint. In contrast, a rise from 201.4 ng/mL to 281.5ng/mL was observed in the DSG group. The differences between both medications were statistically significant, demonstrating a reduction of fibrin products with DRSP.

For the remaining parameters (APC resistance, ATIII activity, and clotting factor VIII), no significant differences were observed between the study groups before and after treatment [38].

Ethics Approval

For each of the investigational centres an ethical approval was obtained. The overall approval for the study with the leading ethical committee was given the 13.07.2012 by the Landesamt für Gesundheit und Soziales Berlin, Geschäftstelle der Ethik Kommission des Landes Berlin, number 11/0606 EK.

EudraCT registration number: 2011-002396-42. Date first subject

Table 3: Baseline data, including blood pressure and body weight in the USA study patient population [37].

		N=1006
Age, years	Mean SD	27.5 (5.94)
	Median	27.0
	Min/Max	18/51
Age group, n (%)	≤35 years	928 (92.2%)
	>35 years	78 (7.8%)
Ethnicity, n (%)	Hispanic or Latino	229 (22.8%)
	Non-Hispanic or Latino	777 (77.2%)
Race, n (%)	American Indian or Alaska Native	13 (1.3%)
	Asian	20 (2.0%)
	Black or African American	358 (35.6%)
	Native Hawaiian or another Pacific islander	5 (0.5%)
	White	571 (56.8%)
	Other	39 (3.9%)
Highest level of education, n (%)	No high school diploma	36 (3.6%)
	High school diploma or equivalent	235 (23.4%)
	Some college	412 (41.0%)
	College degree or higher	323 (32.1%)
Weight group, n (%)	< median weight of the safety set	483 (48.0%)
	≥ median weight of the safety set	523 (52.0%)
BMI group, n (%)	<30 kg/m^2	652 (64.8%)
	≥30 kg/m^2	354 (35.2%)
	>25 to <30 kg/m^2	264 (26.2%)
Blood pressure group	SBP <130 mmHg and DBP <85 mmHg	887 (88.2%)
	SBP ≥130 mmHg and DBP ≥85 mmHg	119 (11.8%)

entered the trial: 01.08.2012.

The date the last subject completed the trial: 27.01.2014.

The protocol was designed and conducted according to existing legal regulations and in accordance with good clinical practice in the conduct of clinical trials and the declaration of Helsinki. All patients gave their written consent for participation in the clinical trial.

Conclusion

Since for treatment with DRSP 4mg in a 24+4 regime over nine complete cycles, no effect on the investigated liver-dependent clotting factors was observed; the novel POP may be regarded as safe concerning its influence on coagulation. As DRSP 4mg is estrogen-free, no enhancing effects on transferrin are expected as well as on D-dimers, both representing important markers in Covid-19 disease.

Covid-19 is currently defined as an immnunothrombotic disease where the clots caused by disseminated intravasal coagulopathy (DIC) may raise up the inflammatory effects responsible for the damages in multiple organs like the lung, the brain, the kidneys.

Also, the fact that a different clinical entity called Long Covid (= "Long Covid" is the denomination to specify the sickness in patients who have either overcome the infection but are still suffering consequences or had the frequent symptoms for far longer than expected) is increasing, e.g., that nearly nine out of 10 patients (87%) discharged from a hospital in Italy still had at least one symptom 60 days after the outbreak. It was pointed out that 13% of the 143 people were completely free of any symptoms, while 32% had one or two symptoms, and 55% had three or more. Although none of the patients had a fever or any signs or symptoms of acute illness, many still reported fatigue (53%), dyspnoea (43%), joint pain (27%), and chest pain (22%). Two-fifths of patients described a lower quality of life [39].

Avoiding factors in contraception that can negatively influence Covid-19 or Long Covid is a new medical need that has to be addressed.

Oestrogen free contraceptives like the newly developed DRSP 4mg preparation may be considered a valuable contraceptive choice for women not only with the disease but also for those at risk of SARS CoV-2 infection or the ones with cardiovascular risk factors.

Conflict of interest: Pedro-Antonio Regidor and Enrico Colli are employees of Exeltis.

Ethical statement: The overall approval for the study with the leading ethical committee was given the 13.07.2012 by the Landesamt für Gesundheit und Soziales Berlin, Geschäftstelle der Ethik Kommission des Landes Berlin, number 11/0606 EK.

Funding

The study mentioned in the manuscript was funded by Insud Pharma, Spain.

Author Contribution

Pedro-Antonio Regidor was responsible for the design of the review and clinical methodology.

Enrico Colli was responsible for the scientific and clinical development program of the oestrogen free contraception.

Acknowledgement

The authors acknowledge Pilar Broch for the support in editing the manuscript.

References

1. Hulswit RJ, de Haan CA, Bosch BJ. Coronavirus spike protein and tropism changes. Adv Virus Res. 2016; 96: 29-57.

2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020; 395: 565-574.

3. Schnittler HJ, Feldmann H. Viral hemorrhagic fever--a vascular disease? Thromb Haemost. 2003; 89: 967-972.

4. Iba T, Levy JH, Thachil J, Wada H, Levi M. Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis. The progression from coagulopathy to disseminated intravascular coagulation in representative underlying diseases. Thromb Res. 2019; 179: 11-14.

5. Iba T, Levy JH, Wada H, Thachil J, Warkentin TE, Levi M. Subcommittee on Disseminated Intravascular Coagulation. Differential diagnoses for sepsis-induced disseminated intravascular coagulation: communication from the SSC of the ISTH. J Thromb Haemost. 2019; 17: 415-419.

6. Woei-A-Jin FJ, van der Starre WE, Tesselaar ME, Rodriguez PG, Nieuwkoop C, Bertina RM, et al. Procoagulant tissue factor activity on microparticles

is associated with disease severity and bacteremia in febrile urinary tract infections. Thromb Res. 2014; 133: 799-803.

7. Gould TJ, Lysov Z, Swystun LL, Dwivedi DJ, Zarychanski R, Fox-Robichaud AE, et al. Canadian Critical Care Translational Biology Group. Extracellular histones increase tissue factor activity and enhance thrombin generation by human blood monocytes. Shock. 2016; 46: 655-662.

8. Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J Thromb Haemost. 2018; 16: 231-241.

9. Suzuki K, Wada H, Imai H, Iba T, Thachil J, Toh CH. Subcommittee on Disseminated In- travascular coagulation. A re-evaluation of the D-dimer cut-off value for making a diagnosis according to the ISTH overt-DIC diagnostic criteria: communication from the SSC of the ISTH. J Thromb Haemost. 2018; 16: 1442-1444.

10. Iba T, Levy JH, Warkentin TE, Thachil J, van der Poll T, Levi M. Scientific and Standardization Committee on DIC, and the Scientific and Standardization Committee on Peri- operative and Critical Care of the International Society on Thrombosis and Haemostasis. Diagnosis and management of sepsis-induced coagulopathy and disseminated intravascular coagulation. J Thromb Haemost. 2019; 17: 1989-1994.

11. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001; 86: 1327-1330.

12. Iba T, Levy JH, Yamakawa K, Thachil J, Warkentin TE, Levi M. Scientific and Stan- dardization Committee on DIC of the International Society on Thrombosis and Haemostasis. Proposal of a two-step process for the diagnosis of sepsis-induced disseminated intravascular coagulation. J Thromb Haemost. 2019; 17: 1265-1268.

13. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol. 2013; 13: 34-45.

14. Delabranche X, Helms J, Meziani F. Immunohaemostasis: a new view on haemostasis during sepsis. Ann Intensive Care. 2017; 7: 117.

15. Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood. 2019; 133: 906-918.

16. Smith SA, Mutch NJ, Baskar D, Rohloff P, Docampo R, Morrissey JH. Polyphosphate modulates blood coagulation and fibrinolysis. Proc Natl Acad Sci USA. 2006; 103: 903-908.

17. Subramaniam S, Jurk K, Hobohm L, Jäckel S, Saffarzadeh M, Schwierczek K, et al. Distinct contributions of complement factors to platelet activation and fibrin formation in venous thrombus development. Blood. 2017; 129: 2291-2302.

18. Noubouossie DF, Reeves BN, Strahl BD, Key NS. Neutrophils: back in the thrombosis spotlight. Blood. 2019; 133: 2186-2197.

19. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. Nat Rev Immunol. 2008; 8: 776-787.

20. Iba T, Levy JH. Derangement of the endothelial glycocalyx in sepsis. J Thromb Haemost. 2019; 17: 283-294.

21. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019. J Clin Invest. 2020; 130: 2620-2629.

22. Huang C, Wang Y, Li X, Ren Li, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel corona- virus in Wuhan, China. Lancet. 2020; 395: 497-506.

23. Nicolai L, Leunig A, Brambs S, Kaiser R, Weinberger T, Weigand M, et al. Immunothrombotic Dysregulation in COVID-19 Pneumonia is Associated with Respiratory Failure and Coagulopathy. Circulation. 2020.

24. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020; 135: 2033-2040.

25. Tang X, Zhiye Z, Fang M, Han Y, Wang G, Wang S, et al. Transferrin plays a central role in coagulation balance by interacting with clotting factors. Cell Research. 2020; 30: 119–132.

26. McLaughlin KM, Bechtel M, Bojkova D, Münch C, Ciesek S, Wass MN, et al. COVID-19-Related Coagulopathy—Is Transferrin a Missing Link? Diagnostics. 2020; 10: 539.

27. Luck AN, Mason AB. Transferrin-mediated cellular iron delivery. Curr Top Membr. 2012; 69: 3–35.

28. Kawabata H. Transferrin and transferrin receptors update. Free Radic. Biol Med. 2019; 133: 46–54.

29. Murakami Y, Saito K, Ito H, Hashimoto Y. Transferrin isoforms in cerebrospinal fluid and their relation to neurological diseases. Proc Jpn Acad Ser B Phys Biol Sci. 2019; 95: 198–210.

30. Tang X, Fang M, Cheng R, Zhang Z, Wang Y, Shen C, et al. Iron-Deficiency and Estrogen Are Associated With Ischemic Stroke by Upregulating Transferrin to Induce Hypercoagulability. Circ Res. 2020; 127: 651-663.

31. WHO Medical eligibility criteria for contraceptive use. 5th edition 2015.

32. PRAC referral assessment report. Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data. Combined hormonal contraceptives containing medicinal products INN: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate. Procedure number: EMEA/H/A-31/1356. 2013.

33. Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, Schweppe KW, et al. Classification and pharmacology of progestins. Maturitas. 2008; 61: 171-180.

34. Schindler AE. Non-Contraceptive Benefits of Oral Hormonal Contraceptives. Int J Endocrinol Metab. 2013; 11: 41-47.

35. Regidor PA, Schindler AE. Antiandrogenic and antimineralocorticoid health benefits of COC containing newer progestins: dienogest and drospirenone. Oncotarget. 2017; 8: 83334-83342.

36. Palacios S, Regidor PA, Colli E, Skouby SO, Apter D, Roemer T, et al. Oestrogen-free oral contraception with a 4 micrograms drospirenone-only pill: new data and a review of the literature. Europ J Contraception & Reprod Health Care. 2020; 25: 221-227.

37. Palacios S, Colli E, Regidor PA. Efficacy and cardiovascular safety of the new estrogen-free contraceptive pill containing 4 mg drospirenone alone in a 24/4 regime. BMC Women's Health. 2020; 20: 218-226.

38. Regidor PA, Colli E, Schindler AE. Drospirenone as estrogen-free pill and hemostasis: coagulatory study results comparing a novel 4mg formulation in a 24þ4 cycle with desogestrel 75 lg per day. Gynecol Endocrinol. 2016; 32: 749–751.

39. Mahase E. Covid-19: What do we know about "long covid"? BMJ. 2020; 370: 2815.