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ORIGINAL RESEARCH ARTICLE

Thromboembolism and Oral Contraceptives During the COVID-19 Pandemic: A Disproportionality Analysis Within the Spanish Pharmacovigilance Database

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Abstract

Background Thromboembolic events (TEs) are known to be a severe complication for COVID-19. They are associated with a systemic inflammatory response syndrome with coagulation cascade activation.

Objective The aim of this study was to determine a potential association between the COVID-19 pandemic and the increment of the risk of suspected TEs in women on systemic hormonal contraceptives (SHCs).

Patients and Methods This study utilised a case/non-case approach in the Spanish Pharmacovigilance Database, which includes more than 290,000 cases of suspected adverse drug reactions (ADRs). The reporting odds ratio (ROR) was calculated during an initial pandemic period in 2020 compared with a pre-pandemic period in 2019 and an additional control period in 2018.

Results While there was a decreased number of ADR notifications for any medications and for any type of ADR in patients on SHCs during the pandemic period, the TE ROR for all SHCs was higher in the 2020 pandemic period [ROR = 11.8 (5.6–24.7)] relative to the pre-pandemic period in 2019 [ROR = 6.3 (3.2–12.5)] and the additional control period in 2018 [ROR = 4.6. (2.1–9.9)]. In contrast, ROR for progestogen-only contraceptives was lower during the pandemic as compared with the two control periods.

Conclusion The reported disproportionality of TEs in women on SHCs rose during the pandemic period. This suggests a potential interaction of the drug (SHC) with COVID-19, which led to an increased risk of TEs in women exposed to both factors. This should be taken into consideration in the context of the COVID-19 pandemic.

1 Introduction

In patients developing sepsis caused by different infectious agents, persistent coagulopathy is a key feature of the disease, and is associated with poor prognosis [1, 2]. Vessel occlusion is one of the underlying mechanisms [3–5]. There is some evidence that COVID-19 promotes the occurrence of thrombotic events (TEs) with varying severity within different vessel territories. Also, COVID-19 has been reported to be able to cause coagulopathy, including disseminated intravascular coagulation (DIC), which is a severe complication that worsens the clinical course of COVID-19 and results in shortened survival [4, 6–9]. The incidence of venous thromboembolism among COVID-19 patients admitted to intensive care units (ICUs) has been reported to be slightly higher than that reported for patients admitted to ICUs with conditions other than COVID-19 [2, 6, 10]. Patients presenting with symptoms suggestive of COVID-19, especially those with the most severe clinical manifestations, have coagulation hyperactivation in addition to the SARS-CoV-2 infection itself. Also, bed stay during a long

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Key Points

The use of estrogens for contraception may be associated with an increased risk of thromboembolic events (TEs), and COVID-19 is likely to promote the development of thrombotic events of varying severity.

In Spain, during the pandemic period of our study, the number of cases of TEs in women on systemic hormonal contraceptives (SHCs) was higher than that observed during the pre-pandemic and the additional control periods. However, this did not hold true for the well-known severe adverse reactions we used as controls (i.e. metamizole-induced agranulocytosis and amoxicillin clavulanic acid-related hepatotoxicity).

This increment of TE reporting in women on SHCs cannot be extrapolated to a true increment of the risk of TE. At any rate, we feel that our findings should be taken into consideration when treating women with SHCs in the context of the COVID-19 pandemic.

period of time may result in increased risk of developing deep venous thrombosis and pulmonary thromboembolism, this risk being particularly high when various combinations of risk factors come together [4, 11].

Concerning the influence of sex, prevalence has been reported to be similar in males and females. However, men with COVID-19 present with more severe disease and higher mortality rates regardless of their age [3, 12, 13].

It is well known that a large number of women worldwide use exogenous estrogen-based contraception. Indeed, oral combined contraception (OCC) represents the most common birth control method, especially among young women. Currently, there is a wide variety of combined estrogen/progestogen preparations available [14, 15].

The use of estrogens is reportedly associated with an increased risk of both venous and arterial thrombosis. Some studies have identified disturbances affecting numerous aspects of the haemostatic and fibrinolytic pathways, with such disturbances promoting the appearance of a prothrombotic milieu [14, 16]. In Spain, some scientific institutions have now released recommendations and clinical algorithms on contraception in women with either suspected or confirmed COVID-19, including the use of progestogens without estrogens combined with low molecular-weight heparin at prophylactic doses [17].

Therefore, it is reasonable to address the potential impact of COVID-19 on the risk of developing TEs in women on OCC and check whether this effect is being accurately reflected by pharmacovigilance databases.

It was the aim of the present study to determine whether there is a potential association between the COVID-19 pandemic and increased risk of reporting suspected TEs in women on systemic hormonal contraceptives (SHCs). The occurrence of such an association would suggest that there is an excess risk of developing these adverse effects due to a potential underlying drug–disease interaction.

2 Method

2.1 Data Mining

We collected data from the Spanish Pharmacovigilance System Database (FEDRA). Data included in this nationwide database are largely accessible to the public and are available for anyone who needs to consult it. FEDRA includes all adverse drug reactions (ADRs) reported to SEFV-H (Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano). Health professionals, the pharmaceutical industry and the public submit notifications of suspected ADRs. Then, ad-hoc committees evaluate these notifications using an algorithm [18] to determine whether a causal relationship exists, though all cases are included in the database regardless of their causality and severity. ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA) [19].

We conducted a search in FEDRA based on the following criteria: (i) spontaneous notifications; (ii) female patients aged between 15 and 50 years; (iii) involvement of a 'hormonal contraceptive for systemic use' (SHC) as the suspected drug; and (iv) occurrence of an adverse reaction coded in the standardised MedDRA query 'embolic and thrombotic events'. The search period covered by the study was from 1 February to 20 September, for the three following periods: 2018, 2019 and 2020.

2.2 Data Statistical Analysis

We used a case/non-case approach to assess the strength of the potential association between any SHCs and TEs [20]. For this purpose, we estimated disproportionality, where the rate at which a particular event of interest (TEs) co-occurs with a given drug (SHC) is compared with the rate this event occurs without the drug in a specific pharmacovigilance database. Cases were defined as notifications of TEs (standardised MedDRA query, 'embolic and thrombotic events'). Non-cases were defined as notifications of reactions other than TEs. Exposure was defined as the recording of an SHC

(ATC Group, G03A) in a report, whether it was suspected of causing the reaction or not.

The strength of the association between TEs and SHCs was estimated by calculating a measure of disproportionality, the reporting odds ratio (ROR) with a 95% confidence interval (CI) and χ^2 with Yates correction (X^2) [21, 22]. This ROR is based on a 2-by-2 contingency table (ROR = $(a/b)/(c/d) = ad/bc$). Thus, a = case-exposed; b = non-case-exposed; c = case-non-exposed and d = non-case-non-exposed. The disproportionality analysis was carried out for three different periods as follows: the pandemic period (1 February to 20 September) and two control periods spanning the same months of the years 2019 and 2018. For the two control periods, the same months were used because we wanted these periods to be as similar to each other as possible. February 2020 was selected as the time point of the pandemic period initiation because, in Spain, the first cases of COVID-19 were officially reported in this month. September 2020 was selected as the month of FEDRA database search completion.

Drugs belonging to the G03A ATC group were included ('hormonal contraceptives for systemic use'). This group comprises four subgroups: G03AA (fixed estrogen/progestogen combinations, referred to as monophasic contraceptives because all the pills contain an equal amount of estrogen and progestogen for all 21 days of the cycle); G03AB (sequential estrogen/progestogen combinations, also known as biphasic and triphasic contraceptives, since they contain both active components—estrogens and progestogens—but in varying amounts depending on the cycle phase); G03AC (containing only progestogen, which are commercialised in both oral and non-oral preparations, such as subcutaneous implants, intrauterine devices and intramuscular injections); and G03AD (progestogens used for emergency contraception). To identify potential differences between contraceptives with and without estrogen, a subgroup analysis was conducted to determine separately the association strength for the G03AA and G03AB subgroups on the one hand, and for the G03AC and G03AD subgroups on the other.

In order to have two well established drug-related adverse events against which to compare the study results, metamizole-induced agranulocytosis and amoxicillin clavulanic acid-related hepatotoxicity were used, since these ADRs are serious and well known in Spain. In addition, they are comparable with TEs and SHCs in terms of their severity and previous knowledge.

3 Results

Results showed that 16,232 and 13,561 reports were submitted to the FEDRA database during the pre-pandemic (2019) and the pandemic period (2020), respectively (Table 1).

Table 1 Reports submitted to FEDRA during February to September of the two periods covered by the study

Reports	2019	2020	Δ (%)[a]
Total FEDRA	16,232	13,561	− 16.5
Women (aged 15–50 years)	2494	2175	− 12.8
Severe	818	705	− 13.8
SHC[b]	159	144	− 9.4
Thromboembolic events	12	13	8.3

[a]Variation percentage

[b]Systemic hormonal contraceptives included in the G03A (ATC) group

FEDRA Spanish Pharmacovigilance System Database, *SHC* systemic hormonal contraceptive

Therefore, there was a 16.5% drop during the latter period. Of 16,232 reports submitted within 2019, 2494 corresponded to women aged between 15 and 50 years, and 159 of them were on SHCs included in the G03A subgroup, with 12 cases of TEs reported ($n = 12$). In 2020, 13,561 ADRs were reported, of which 2175 corresponded to women aged 15–50 years; 144 of them were exposed to SHCs belonging to the G03A subgroup, with 13 cases of TEs reported ($n = 13$).

Concerning patients' age, there was a minimal variation between the pre-pandemic (2019) and the pandemic periods (2020). The median age was 31 years (range 15–43) and 25.5 years (range 17–49) in 2020 and 2019, respectively.

All cases were severe in both periods (pre-pandemic 2019 and pandemic 2020), and in one case notified during the pandemic period the clinical outcome was fatal. The profile of the most frequently reported TEs varied slightly in the pandemic (2020) relative to that in the pre-pandemic period (2019) since there were twice as many cases of pulmonary thromboembolism in 2020 (9/13 cases) compared with 2019 (4/12 cases). In contrast, there were more cases of cerebral thrombosis in 2019 than in the pandemic period (5/12 and 2/13 cases, respectively). Only two of the 13 cases reported in 2020 included data on COVID-19, and in these two cases PCR testing proved negative.

It is of note that in the 2019 and 2020 study periods, some of the cases presented other potential contributing factors, such as obesity, smoking habit, coeliac disease, Horn syndrome, permanent foramen ovale and sclerosis of the lower limbs.

The statistical analysis results (Table 2) yielded the values for ROR (95% CI) and X^2 disproportionality estimators. These estimators were higher for the group comprising all SHCs in the 2020 pandemic period [ROR = 11.8 (95% CI 5.6–24.7)] relative to the 2019 pre-pandemic period [ROR = 6.3 (95% CI 3.2–12.5)] as well as to the 2018 control period [ROR = 4.6 (95% CI 2.1–9.9)]. This trend was maintained when the subgroups of estrogen/progestogen

Table 2 Disproportionality analysis for SHCs and TEs identified

ATC group	2018			2019			2020		
	N	ROR (95% CI)	X^2	*N*	ROR (95% CI)	X^2	*N*	ROR (95% CI)	X^2
Systemic hormonal contraceptives	9	4.6 (2.1–9.9)	15.5	12	6.3 (3.2–12.5)	31.6	13	11.8 (5.6–24.7)	60.4
Estrogen–progestogen combinations	9	7.9 (3.6–17.3)	32.9	9	8.1 (3.7–17.5)	34.5	12	17.4 (8.1–37.4)	88.5
Progestogen only	0	NA	NA	3	2.7 (0.8–9.1)	1.6	1	1.4 (0.2–10.4)	NA

ATC anatomical, therapeutical and chemical classification, *CI* confidence interval, *N* number of cases, *NA* not applicable, *ROR* reporting odds ratio, *SHCs* systemic hormonal contraceptives, *TEs* thrombotic events, X^2 Chi-square–Yates correction

Table 3 Disproportionality analysis for metamizole-induced agranulocytosis and amoxicillin clavulanic acid-related hepatotoxicity

Drug—ADR	2019			2020		
	N	ROR (95% CI)	X^2	*N*	ROR (95% CI)	X^2
Metamizole—agranulocitosis	9	15.7 (7.0–35.2)	69.6	3	12.0 (3.3–44.1)	15.0
Amoxicillin + clavulanic acid—hepatotoxicity	4	6.2 (2.1–18.2))	10.1	2	1.9 (0.4–7.8)	NA

ADR adverse drug reaction, *CI* confidence interval, *N* number of cases, *NA* not applicable, *ROR* reporting odds ratio, X^2 Chi-square–Yates correction

combinations (G03AA + G03AB) were analysed separately. However, when analysing the progestogen-only contraceptive subgroup, we found non-significant disproportionality with three cases in 2019, since in 2020 there was only one case, and there were no cases in 2018. These differences did not reach statistical significance for disproportionality.

Concerning control associations (Table 3), the cases of metamizole-induced agranulocytosis found in the FEDRA database were used to estimate the corresponding disproportionality estimators, which yielded an ROR value of 12.0 (95% CI 3.3–44.1) and X^2 of 15.0 for the pandemic period in 2020. These figures are smaller than those corresponding to the same period in 2019 [ROR = 15.7 (95% CI 7.0–35.2) and X^2 = 69.6]. With regard to the other control association (i.e. amoxicillin + clavulanic-related hepatotoxicity), the ROR value was 1.9 (95% CI 0.4–7.8) and X^2 was not applicable because there were only two cases, and ROR was 6.2 (95% CI 2.1–18.2) and X^2 was 10.1 for both periods, respectively.

4 Discussion

Our findings show a 16.5% decrease in the reports submitted to SEFV-H during the pandemic period compared with the number of reports submitted in 2019. This drop was also noted when restricting the search to adolescent and adult female patients (aged 15–50 years). This age range was selected because it comprised the largest proportion of the target population and because it is reasonable to assume that therapy with estrogens and progestogens has an indication other than contraception in females younger than 15 or older than 50 years. In addition, we encountered a decreased number of reports within this population group when the search was limited to severe reactions (−13.8%) and patients on any SHCs (−9.4%). These findings are in line with what was reasonable to expect during the pandemic because of the high care workload and the resultant severe overcrowding in both primary healthcare centres and hospitals, particularly resulting from management of mild and moderate COVID-19 cases. Strikingly, the number of TE cases reported during the COVID-19 pandemic increased by 8.3%, and they were all severe.

Given that, in general, there were fewer notifications during the pandemic period, it is likely that mild ADR reporting decreased, while, on the contrary, both severe and unknown reactions continued to be notified as previously. Likewise, we assume that reactions to newer drugs continued to be reported. Consequently, there may have been a drop in reports involving mild and known ADRs associated with old drugs. On the contrary, reporting of severe ADRs might have continued, even when well-known ADRs (e.g. SHC-related TEs) were involved. This is the reason why we used the disproportionality measures of metamizole-induced agranulocytosis and amoxicillin clavulanic acid-related hepatotoxicity, since they are well-established severe ADRs that have been known about for a long time, as controls for ADR–drug associations. We also observed a drop in the number of notifications for controls, a finding that challenges the above hypothesis. While during the pandemic period we found higher disproportionality value estimators for the well-known severe ADR 'SHC-related TEs', this increment was not observed for the ADR–drug associations 'metamizole-induced agranulocytosis' and 'amoxicillin clavulanic

acid-related hepatotoxicity'. Indeed, the disproportionality value for the latter dropped (Table 3).

Our results show that there was one case more during the first period of the pandemic (i.e. 2020) than in 2019. However, there were four cases more than in the additional control period (2018), in the context of a general decrease in reporting due to the healthcare system standstill caused by the pandemic in Spain. The statistics ROR and X^2 showed an increased disproportionality during the pandemic period (2020) compared with the immediate pre-pandemic (2019) and the additional control (2018) periods. Nevertheless, this difference proved not to be statistically significant.

The TE profile was different during the COVID-19 pandemic. Thus, we found an increase in pulmonary thromboembolism incidence, whereas cerebral thrombosis was the predominant thrombotic event during the previous year. When investigating the cases of cerebral thrombosis, it was noted that there were potential alternative causes, such as cardiomyopathy, Horner syndrome, persistent foramen ovale, coeliac disease and personal history of stroke.

It was reasonable to expect an increase in TE incidence during the pandemic period due to the joint impact of a variety of factors, such as COVID-19 itself and the sedentary lifestyle associated with stay-home measures. Still, in the population under investigation, we observed a decline in the number of reported TEs associated with a broad variety of medications—excluding oral contraceptives (i.e. cases in non-exposed patients).

With regard to the association under investigation, our results indicated that disproportionality was higher within the pandemic period as compared with the control period for all the SHC subgroups (ATC Group G03A). The greatest difference between both periods corresponded to oral contraceptives (estrogen/progestogen combinations) (Table 2).

A combination of estrogens and progestogens was first approved in 1957 in the United States for treatment of menstruation disturbances. Later, in 1960, this combination was approved as a contraceptive agent. In the 1970s, an association of the estrogen dose to thrombosis was established. For this reason, the manufacturers reduced the amount of estrogen in the pill, and this reduction was followed by a decreased incidence of thrombosis. The increased risk of TEs associated with SHCs has been broadly documented [23–29]. There is strong evidence that the risk is associated principally with estrogens, and exposure duration is known to play an important role. The risk usually diminishes after the first year of treatment [14, 27, 30, 31]. It has been put forward that progestogens exert a modulating action, and several studies have failed to find an increased risk of TEs in women taking contraceptive pills containing only progestogens in comparison with those who did not take a contraceptive agent [32–34]. This agrees with our findings, since, in the present study, disproportionality for 'only progestogens' was not statistically significant in either of the periods under investigation.

Concerning the disproportionality estimators, good signal detection practices require at least three cases for ROR estimation. Nonetheless, this is a simple recommendation that is applied only with the purpose of detecting signals, that is, new associations between a given drug and a specific ADR. In the present study, it was in no way our intention to identify a signal. The aim of our study was solely to compare the notified cases of the ADR in question in different periods. For the group of progestogens (Table 2), ROR was estimated in order to stratify the systemic contraceptives by subgroup and try to find any potential differences. It should be borne in mind that the ROR statistic can be estimated whenever the number of cases is >0. On the other hand, for X^2-Yates (i.e. X^2 test with Yates correction), we recorded NA (not applicable) when a box of the 2-by-2 contingency table included a value <3.

In our series, all the TE cases were deemed to be severe. During the 2020 pandemic period, 53.8% of TE cases were notified from a hospital, unlike in the pre-pandemic period 2019, in which only 16.7% of cases were reported from the hospital setting. However, no cases of COVID-19 were reported, which suggests that none of these patients had a positive PCR (polymerase chain reaction) test. If this were the case, our hypothesis of a potential interaction would be challenged. However, it should be taken into account the problems with conducting PCR testing in patients with suspected COVID-19 at that time in Spain. There is an important gap of dozens of thousands of people between official data on mortality potentially due to COVID-19 and those from MoMo (monitored mortality). Because official statistics only include PCR-positive cases, MoMo data should be considered more reliable to establish the actual COVID-19 mortality. This broad disparity suggests that PCR testing was not undertaken in many patients, even in those cases in which there was suspicion that the fatal clinical outcome was due to infection by SARS-CoV-2. Furthermore, the risk of TE is particularly high at the end of the infection, and the PCR test is likely to be negative at this late stage. Lastly, it should be taken into account that data on diagnostic tests are very often lacking in suspected ADR notification forms, which may have negatively affected our result reliability.

We found an increase in the value of ROR and χ^2 estimators for SHCs and SHC combinations during the pandemic period, which speaks in favour of a potential interaction between COVID-19 and the use of SHC that would result in increased TE risk. However, we are aware that our findings are not sufficiently sound to state that there has been an actual increase in the reporting of the ADRs under investigation. At any rate, it should be kept in mind that our purpose was simply to verify that the number of notified cases of suspected interaction between SHCs and TEs was

disproportionately larger than the number of the remaining ADRs related to any medications when considering both any kind of ADR in general and any type of TE in particular (i.e. TEs related to any other medications).

4.1 Limitations

Spontaneous reporting of suspected ADRs has some drawbacks such as under-reporting, which, though hard to be accurately estimated, has been reported to be as high as 90% [35]. An additional limitation is the fact that the number of reports submitted to the databases strongly relies on factors such as the drug in question (time elapsed since it was first commercialised, clinical use, knowledge and so forth), and the profile of the reporting person (time availability, commitment, training in the field of pharmacovigilance, etc.). Additionally, the relevance and impact of these limiting factors may vary with time or other circumstances. At any rate, spontaneous reporting of ADRs presents a number of advantages: it is a simple, quick and economical method enabling generation of hypotheses and identification of new potential safety concerns involving drugs—notably rare, infrequent or unexpected events. Healthcare professionals, pharmaceutical companies and the public should be aware of how important is to report any suspected ADRs. Therefore, the clinician prescribing a SHC should keep a careful track of treatment, especially during the first months. Likewise, he/she should discuss with the patient the symptoms and signs indicative of TE, so that women can identify them and report to their physicians promptly, which in turn would enable the prescriber to notify the ADR quickly and efficiently. Lastly, research on suspected ADRs in no way can substitute cause–effect studies. Still, research on spontaneous reporting enables us to address potential associations between the reported medication and a particular suspected ADR, as well as to compare the observed versus expected reaction and analyse its timing pattern and temporal evolution. Based on the results in the present study, we have generated a hypothesis that may be clinically relevant. Though not a causal relationship, the data we obtained enable us to establish a relation between the COVID-19 pandemic and increased risk of TEs in women on SHCs.

4.2 Conclusions

A potential new drug/disease (SHC/COVID-19) interaction might result in increased reporting of TEs in women on SHCs, as suggested by the increment in the disproportion of reported cases of TEs found during the pandemic period. This indicates that there is a need for this potential risk to be monitored. The use of estrogens for contraception is associated with an increased risk of TE, and COVID-19 is likely to promote the development of thrombotic events of varying severity. In Spain, during the pandemic period of our study, the disproportion of reported cases of TEs in women on SHCs was higher than that observed during the pre-pandemic and the additional control periods. However, this did not hold true for the well-known severe adverse reactions we used as controls (i.e. metamizole-induced agranulocytosis and amoxicillin clavulanic acid-related hepatotoxicity). At any rate, we feel that our findings should be taken into consideration when treating women with SHCs in the context of the COVID-19 pandemic.

4.3 Statement

FEDRA is the Spanish Pharmacovigilance System of Human Medicines (SEFV-H) database and is managed by the Spanish Medicines and Health Products Agency (AEMPS). The information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The discussion and conclusions of this study are the authors' responsibility and do not represent the opinion of the SEFVH or the AEMPS.

Declarations

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Conflicts of interest/competing interests None.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The data supporting the findings in this study are available from the Spanish Pharmacovigilance System (SEFV-H). Restrictions apply to the availability of these data, which were provided by the SEFV-H. Data are available from the authors with the permission of SEFV-H.

Code availability Not applicable

Authors' contributions LM conceptualised and designed the study, RS acquired data, LM, EN, RS, MS and IS analysed, drafted, reviewed and approved the manuscript.

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