

CLINICAL ARTICLE

Obstetrics

Thromboembolic events in pregnant and puerperal women after COVID-19 lockdowns: A retrospective cohort study

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Abstract

Objective: To explore the indirect impact of the COVID-19 pandemic on patterns of pregnancy-related venous thromboembolism (VTE) events, mediated by population mobility restrictions during lockdown periods.

Methods: Pregnancy-related VTE hospitalizations were identified through a code-targeted search of the Hadassah Medical Center's computerized database. A manual analysis of relevant medical records was performed, and cases diagnosed throughout the year 2020 were compared to those diagnosed during 2019 and 2018. Statistical analyses studied obstetrical outcomes, as well as the extent and treatment of VTE events during the COVID-19 pandemic compared to those of preceding years, stratified by pre-, intra-, and post-lockdown periods.

Results: The incidence of pregnancy-related thromboembolic events during 2020 was 0.16% of all deliveries, significantly higher than in 2018 and 2019 (0.06% and 0.1%, respectively; $P < 0.05$). Higher rates of VTE events were found during post-lockdown periods in 2020, compared with corresponding time periods in 2019 and 2018.

Conclusion: The present data suggest that lockdown periods impact pregnancy-related VTE hospitalizations, possibly as a result of restricted population mobility. Increased awareness of this undesirable outcome may aid health policymakers in the continuing struggle with epidemics.

KEYWORDS

coronavirus, deep vein thrombosis, immobilization, pandemic, pregnancy, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE) is a disease that manifests as deep venous thrombosis (DVT) or pulmonary embolism. Although VTE during pregnancy and the puerperium is an infrequent event,¹

the risk of VTE events during this period was found to be four- to fivefold higher than that in non-pregnant women.² Furthermore, in the Western world, it has been either the leading cause of maternal death or ranked closely behind sepsis and pre-eclampsia/eclampsia.³

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The risk of VTE events increases as the pregnancy progresses, peaking in the postpartum period. Approximately 80% of pregnancy-associated VTE events are DVTs, half of which occur during the postpartum period. When occurring during pregnancy, under the influence of estrogen, DVT is more likely to be proximal, massive, and in the left extremity.²

The causes for VTE are presented in Virchow's triad: hypercoagulability; vascular damage; and venous stasis. Pregnancy is a state characterized by all three conditions, thereby increasing the risk of VTE events among pregnant and postpartum women.⁴

Hypercoagulability is the main reason for the increased risk of thromboembolism during pregnancy, as pregnancy is, by definition, a hypercoagulable state. Normal hemodynamic changes occurring during pregnancy include increased levels of clotting factors, decreased levels of natural anticoagulants, and diminished fibrinolytic activity. These changes facilitate normal placental function during pregnancy and prevent excessive bleeding during delivery, yet at the same time predispose to thrombosis.⁵ Venous stasis in pregnancy results from dilation of the lower extremity veins, followed by venous compression by the gravid uterus and enlarging iliac arteries. Circumstances characterized by limited mobility (such as surgery, cesarean delivery, bed rest, or air travel) may further elevate this risk.⁶ Findings from the RIETE registry, in which more than 10000 women who presented with acute VTE had been enrolled, concluded that one in every four pregnant women developed VTE shortly after surgery or prolonged immobility.¹

Although numerous publications studied the direct COVID-19-associated coagulopathy,⁷ the present study focused on the less-studied potential indirect effect of the pandemic on pregnancy-related VTE morbidity. Many countries have taken measures to limit personal mobility in order to prevent the spreading of COVID-19. Yet, it is believed that no study has explored the impact of immobilization during lockdown periods on pregnancy-related VTE events.

The aim of the present study was to determine whether the COVID-19 pandemic is associated with a higher incidence of pregnancy-related VTE events, unrelated to COVID-19 infection. It was hypothesized that a pattern may be suggested, associated with lockdown periods.

2 | MATERIALS AND METHODS

Pregnancy-related VTE hospitalizations throughout the year 2020 were investigated and compared to hospitalizations in 2018 and 2019. Cases were identified through a code-targeted search of the Hadassah computerized database. In this database, all diagnoses are classified according to the International Classification of Diseases, 9th revision (ICD-9). The search included both Hadassah campuses: Mount Scopus and Ein Kerem medical centers.

The Hadassah-Hebrew University Medical Center provides comprehensive medical care for roughly 1.5 million patients annually, mainly from Jerusalem and the surrounding areas. Hadassah has

two campuses, at Ein Kerem and Mount Scopus, that together offer 1200 hospital beds and 40 hybrid and advanced operating rooms.⁸ Hadassah Hospital Ein Kerem in the west of the city has over 130 departments and clinics and is a tertiary level hospital and national referral center for challenging and complex cases. Hadassah Mount Scopus serves the heavily populated Jewish and Arab neighborhoods of northern and eastern Jerusalem with over 30 departments and clinics. Together, the annual number of deliveries is 13 000, 15% of which are delivered by cesarean section. Both campuses together account for 40% of the annual deliveries in Jerusalem.

Inclusion criteria were: pregnant or puerperal (up to 6 weeks postpartum or after miscarriage or pregnancy termination) women, aged 18–45 years, who were diagnosed with pulmonary embolism, DVT, or ovarian vein thrombosis (OVT) during the years 2018–2020. Cases of superficial vein thrombosis (SVT), ambulatory-treated cases, and cases involving an inconclusive diagnosis were excluded.

All cases of pregnant or puerperal women were analyzed. The medical record of each patient was reviewed in its entirety. Since all patients were screened for COVID-19 as a hospital policy starting in March 2020, swabs (polymerase chain reaction [PCR]) or serological test results were available in most cases in 2020 (16 of 21).

The first lockdown in Israel commenced on March 15 and ended on April 29. In predominantly Muslim areas, it continued until May 3 (due to the Ramadan holiday). The second lockdown commenced on September 18 and ended on October 11. Restrictions varied throughout inter-lockdown periods, with mobility being still limited compared to parallel time periods in the preceding years.

Comparison of the cases of pregnancy-related VTE was performed on the annual level (to estimate the overall differences in pregnancy-related VTE hospitalizations, as well as demographic, obstetrical, and therapeutic characteristics). Hospitalizations during 2020 were compared to the 2 preceding years. The incidence of VTE was also compared by calendar month in order to limit the effect of seasonality and further characterize the impact of national lockdowns on the incidence of VTE.

Statistical analyses were performed in Python 3.7.6, using the Pandas 1.0.1 and SciPy 1.4.1 libraries. Quantitative variables were compared by the Kruskal-Wallis test. Categorical variables were compared using the χ^2 test. Statistical significance was set at $P < 0.05$.

The present study was approved by the Hadassah Institutional Review Board in accordance with the Helsinki declaration.

3 | RESULTS

Over 1500 files were screened of women with a diagnosis of DVT, OVT, SVT, and pulmonary embolism, related and unrelated to pregnancy, hospitalized in Hadassah Medical Center between the years 2018 and 2020. After the exclusion of duplicates, 394 cases were reviewed before entering them into the final database. A total of 21 cases met the inclusion criteria during 2020, nine cases during 2019, and 13 cases during 2018.

TABLE 1 Demographic and obstetrical characteristics of patients with pregnancy-related VTE during the years 2018–2020.^a

	2020 (n=21)	2019 (n=9)	2018 (n=13)	P value
Maternal age (years)	31.6±7.4	32.8±5.7	29.1±4.2	0.362
Weight (kg)	74.0±10.3	78.2±17.6	72.8±12.1	0.803
Gravidity	4.5±2.8	3.4±1.5	3.0±1.9	0.260
Parity	2.7±2.2	2.0±1.4	1.8±1.7	0.487
Gestational age at diagnosis (weeks)	18.6±11.4	22.6±13.6	20.2±10.8	0.820
Risk factors ^b	3.3±1.8	2.7±1.3	2.4±1.2	0.333
Smoking (%)	9.5	11.1	7.7	0.962
Thrombophilia (%)	28.6	11.1	23.1	0.583
TOP in index pregnancy (%)	19.0	0.0	15.4	0.379
VTE post CS (%)	28.6	22.2	7.7	0.345
VTE post vaginal delivery (%)	4.8	11.1	15.4	0.571
Clexane daily dosage (mg)	164.8±39.9	160.0±30.2	150.7±41.3	0.613
IVC filter (%)	9.5	22.2	15.4	0.644
Thrombolysis (%)	9.5	22.2	15.4	0.644
DVT (%)	76.2	33.3	76.9	0.048
OVT (%)	9.5	33.3	0.0	0.051
PE (%)	19.0	44.4	23.1	0.333
Left side (%)	61.9	55.6	69.2	0.802
Duration of hospitalization (days)	7.3±5.2	16.3±8.49	6.2±5.3	0.006
Positive COVID-19 PCR (%)	4.7 ^c			-
Overall incidence of VTE (as a share of annual deliveries) (%)	0.16	0.06	0.1	<0.05

Abbreviations: CS, cesarean section; DVT, deep vein thrombosis; IVC, inferior vena cava; OVT, ovarian vein thrombosis; PCR, polymerase chain reaction; PE, pulmonary embolism; TOP, termination of pregnancy; VTE, venous thromboembolism.

^aValues are given as percentage or mean ± SD; the significance for differences was measured using the χ^2 and Kruskal–Wallis tests.

^bRisk factors are defined as pregnancy, postpartum period, post CS, age >35 years, parity >6, concurrent infection, multifetal pregnancy, hypertensive disorder of pregnancy, postpartum hemorrhage or blood transfusion, thrombophilia, hyperemesis gravidarum, smoking, family history of VTE, personal history of VTE, or co-morbidity.

^cCOVID-19 PCR results were available for 16 of 21 patients.

The incidence rate of VTE events, defined as the number of annual VTE events divided by the number of annual deliveries, was significantly higher in 2020 compared to 2019 and to 2018 (0.16% during 2020 vs 0.06% and 0.1% in 2019 and 2018, respectively; $P < 0.05$). Table 1 depicts the demographic and obstetrical characteristics of these patients. No statistically significant difference was found when comparing the demographic and obstetrical characteristics of cases diagnosed in the different years. Similarly, no differences were noted in the extent of the thromboembolic events or their treatment, although the length of hospitalization was significantly longer in 2019.

In an attempt to visualize the possible effects of lockdowns on the incidence of VTE incidence, the calendar year was subdivided into three time periods, according to the mobility restrictions that were enforced during 2020 in Israel: January and February were considered pre-lockdown periods; March, April, and September were considered lockdown periods; and May to August and October to December were considered post-lockdown periods. As shown in

Figure 1, a significant difference in the incidence of VTE during the post-lockdown period was noted (0.23% for 2020, 0.07% and 0.09% for 2019 and 2018, respectively; $p < 0.05$). No such difference was observed during the pre-lockdown or lockdown periods (Figure 1).

Figure 2 demonstrates the cumulative incidence of thromboembolic events during 2018 to 2020 in absolute values. The figure illustrates the two periods of sharp rises in the number of cases after lockdown periods during 2020, a finding not observed in 2018 or 2019.

No evidence was found suggesting that COVID-19 infection itself was a cause of the observed VTE events during pregnancy. Of the 21 VTE events in 2020, only one patient (constituting 4.7% of the cases of VTE in 2020) had tested positive for SARS-COV-2 (nasopharyngeal PCR), 3 months before her documented diagnosis of a thromboembolic event. The patient was a 34-year-old woman, admitted with persistent fever during the postpartum period after an emergency cesarean delivery. A computed tomography scan demonstrated right OVT, a small spleen infarction, and fluid collection

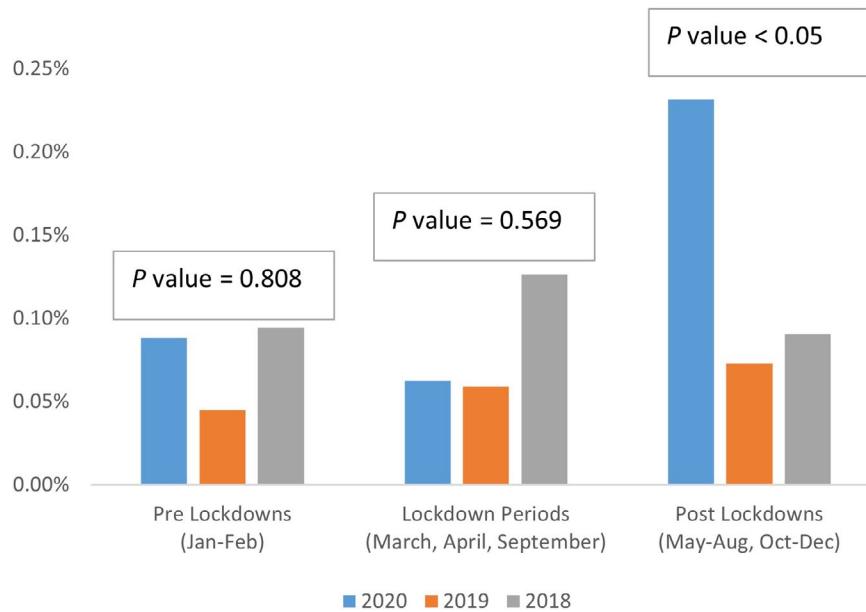


FIGURE 1 Incidence of hospitalized cases of pregnancy-related venous thromboembolism stratified by lockdown status in 2020 and compared with 2018–2019.

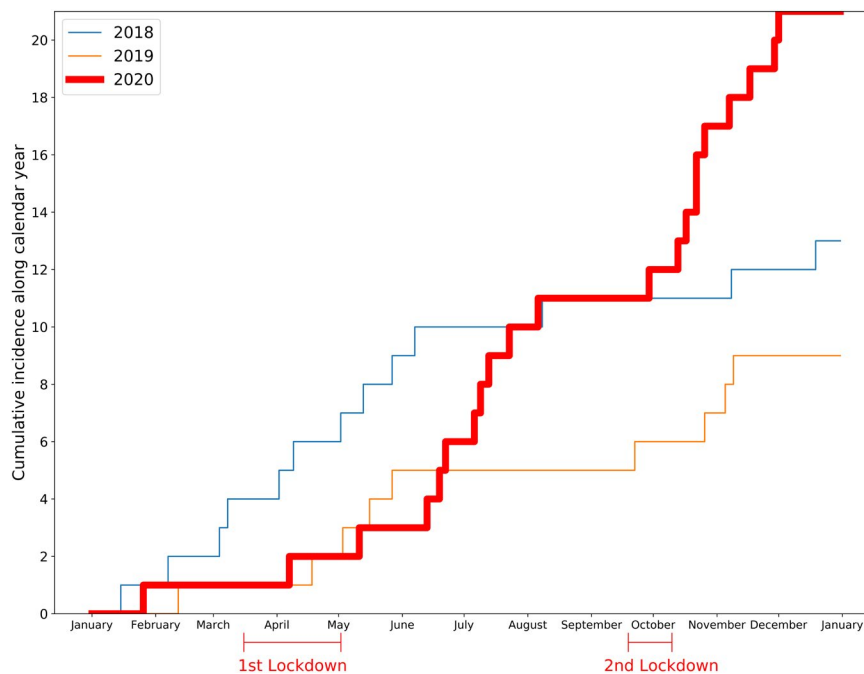


FIGURE 2 Cumulative incidence of cases of pregnancy-related venous thromboembolism during 2018–2020.

proximal to the surgery scar. The collection was drained and the patient was treated with antibiotics and low-molecular-weight heparin (100 mg twice daily). Antiphospholipid antibody tests returned positive during hospitalization. All other included patients (admitted during the year 2020) with available PCR tests results were negative for COVID-19.

4 | DISCUSSION

The year 2020 was characterized by a higher incidence of pregnancy-related VTE events necessitating hospitalizations compared to previous years. This higher rate was evident specifically during the two post-lockdown periods, suggesting a lag effect

of population immobility resulting from the national lockdown restrictions.

No statistically significant differences were noted in demographic or obstetrical characteristics, nor in clinical course, severity, or treatment approaches, compared to cases analyzed from preceding years. These findings suggest an independent association between immobilization and VTE events rather than a confounded one. Although the length of hospitalization was significantly longer in 2019, this fact may not represent the extent or severity of the thromboembolic event itself but rather the existence of synchronous medical conditions.

The increase in cases of pregnancy-related VTE during 2020 may reflect several underlying factors, apart from the general restrictions imposed during lockdown periods. First, inter-lockdown periods were also marked by decreased mobility compared to parallel periods in previous years. Second, it is plausible that the restricted mobility throughout the year had an additive effect, causing the second lockdown to appear as having had a greater impact on the incidence of VTE when compared to the first lockdown. Lastly, pregnant women may have been even less active than the general population in attempt to reduce exposure due to concerns and uncertainties surrounding the specific impact of COVID-19 on pregnancy.^{9,10}

It should also be noted that the small number of cases diagnosed during the first lockdown (Figure 2) may have been a result of the decrease in non-COVID-19 hospital admissions during that period, reported by hospitals around the world.¹¹⁻¹⁴

Importantly, although previous studies reported an association between COVID-19 infection per se and VTE events in the non-pregnant population, the findings of the present study are independent of this phenomenon as COVID-19 infection was ruled out in the vast majority of cases (one case excluded).

The main strength of the present study is in its novelty. It is believed that this is the first study to examine an indirect implication of COVID-19 on public health and specifically on pregnant women, potentially resulting from restrictions imposed by authorities in Israel and in many other countries.

Another strength of the present study is the meticulous and detailed manual analysis of each medical file containing any relevant diagnosis, thus minimizing margins of error compared to a solely keyword-based search.

On the other hand, the small number of cases of pregnancy-related VTE has limited the ability to identify small but significant differences in severity and therapeutic option characteristics among relevant cases over the studied years.

Another limitation to note is that women diagnosed recently (i.e. in 2020) have not yet completed their hypercoagulability investigation, while older cases have (2018-2019).

Furthermore, being a retrospective medical file-based study, the lack of information due to incomplete documentation made it difficult to perform an accurate analysis of demographic characteristics (for instance, missing data regarding body mass index).

5 | CONCLUSION

To conclude, the COVID-19 pandemic appears to bear indirect effects that spread beyond the immediate and intuitive ones. National lockdowns may result in health implications for the public in general and specifically for pregnant women. The present study suggests an association between national lockdowns resulting in relative immobilization and an increase in the incidence of pregnancy-related VTE events.

As VTE in pregnant women can be a life-threatening event, it is felt that the findings of the present study should be incorporated into continued health-policy recommendations. Maintaining an active lifestyle, especially during pregnancy and regardless of national lockdowns, may prove to have a paramount impact on maternal health. The importance of avoiding immobility in times of either lockdown or quarantine should be stressed and translated into practical assistance.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

ACP and DB contributed equally. Both authors planned the study, performed manual data collection and data analysis, wrote and edited the manuscript. AW conceived the original idea of the study and was in charge of overall direction and planning, discussed, commented, edited and finally approved the manuscript. HA was involved in planning the design of the study, supervised the work, discussed, commented, edited and finally approved the manuscript. KM participated in data collection, discussed, commented, edited and finally approved the manuscript.

TS participated in the manual data collection, planning the design of the study, supervised the work, discussed, commented, edited and finally approved the manuscript. YK was involved in planning the design of the study, supervised the work, discussed, commented, edited and finally approved the manuscript. YL was involved in planning the design of the study, supervised the work, discussed, commented, edited and finally approved the manuscript.

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