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Original Contribution

Current use of estrogen-containing oral contraceptives or hormone therapy and risk of COVID-19 infection and hospitalization: a population-based cohort study

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Abstract

The association between current use of oral contraceptives (OCs) among women younger than 50 years ($n = 306\,541$), and hormone therapy (HT) among women aged 50 years or older ($n = 323\,203$), and coronavirus 2019 (COVID-19) infection and hospitalization was evaluated in this population-based cohort. Current OC/HT use was recorded monthly using prescription dispensing data. COVID-19 infections were identified from March 2020 through February 2021. COVID-19 infections and hospitalizations were identified through diagnosis codes and laboratory tests. We used weighted generalized estimating equations models to estimate multivariable adjusted odds ratios (aORs) for COVID-19 infection associated with time-varying OC/HT use. Among women with COVID-19, logistic regression models were used to evaluate OC/HT use and COVID-19 hospitalization. Over 12 months, 11 727 (3.8%) women younger than 50 years and 8661 (2.7%) women aged 50 years or older experienced COVID-19 infections. There was no evidence of an association between OC use and infection (aOR = 1.05; 95% CI, 0.97-1.12). There was a modest association between HT use and infection (aOR = 1.19; 95% CI, 1.03-1.38). Women using OCs had a 39% lower risk of hospitalization (aOR = 0.61; 95% CI, 0.38-1.00), but there was no association of HT use with hospitalization (aOR = 0.89; 95% CI, 0.51-1.53). These findings do not suggest a meaningfully greater risk of COVID-19 infection associated with OC or HT use. OC use may be associated with lower COVID-19 hospitalization risk.

Key words: COVID-19; SARS-CoV-2; oral contraceptives; hormone therapy; hormones; population-based cohort study.

Introduction

Throughout the coronavirus 2019 (COVID-19) pandemic, rates of severe outcomes such as hospitalization and death have been higher in men than women.[1-4] It is unclear whether these sex differences are due predominantly to biological differences in endocrinology and immune response, differences in comorbid conditions, or behavioral differences that led to different infection rates in men and women.[5] It is plausible that sex differences in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 severity may be associated with differences in endogenous estrogen levels, which are higher among premenopausal women than postmenopausal women or men.[1] Mechanisms by which higher estrogen levels might reduce the risk of SARS-CoV-2 infection and severe outcomes include the roles of endogenous sex steroid hormones in viral entry and detection,[3] immune response,[4] and inflammation.[4] The entry receptor for SARS-CoV-2, angiotensin-converting enzyme 2,[6] is downregulated by endogenous estrogens.[3,6-8] Estrogen also decreases expression of cellular transmembrane serine protease 2, which enhances entry of SARS-CoV-2.[3,9-12] Endogenous sex hormones also modulate the production of interferon-α, which supports detection of SARS-CoV-2.[3,13] Furthermore, estrogen receptors are expressed in all immune cells,[4] and estrogen is involved in the inhibition of proinflammatory cytokine production.[4]

Based on these potential mechanisms, use of exogenous oral contraceptives (OCs) or hormone therapy (HT) may also be associated with a lower risk of COVID-19 infection and severe outcomes. However, use of OCs or HT is associated with greater risk of thrombotic events, such as venous thromboembolism,[14-17] and COVID-19 has also been positively associated with venous thromboembolism risk,[18] leading to concern that OC or HT use among women with COVID-19 might increase the risk of severe outcomes such as hospitalization or death. Early in the pandemic,

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this concern led some medical professional organizations to recommend the discontinuation of OCs or HT by women hospitalized with COVID-19.[19-21] Issued before evidence about these possible associations was available, this clinical guidance highlights the need for improved understanding of the association between estrogen-containing OCs or HT and risk of COVID-19 infection and hospitalization.

Two European studies have evaluated OC or HT use in relation to COVID-19 infection and hospitalization, but follow-up for these studies ended in May or June 2020, before widespread availability of nucleic acid amplification tests, meaning there may have been misclassification of COVID-19 outcomes. Both studies relied on self-reported OC and HT exposure and COVID-19 outcome data, which may lead to misclassification and biased results.[22,23] Results were inconsistent, with 1 study reporting a lower COVID-19 infection risk with OC use but a higher risk with HT use[22] and the second study finding no evidence of an association between current or recent OC or HT use and a SARS-CoV-2–positive nasal swab.[23]

We conducted a population-based retrospective cohort study to evaluate whether current use of estrogen-containing OCs versus nonuse was associated with the risk of COVID-19 infection among women younger than 50 years and, similarly, whether current HT use was associated with infection risk among women aged 50 years or older. Among women with COVID-19, we evaluated the association between current use of estrogen-containing OCs versus nonuse and the risk of hospitalization in women younger than 50 years and the association between current use of estrogen-containing oral HT versus nonuse and the risk of hospitalization in women aged 50 years or older. We hypothesized that current use of OCs or HT would be associated with a lower risk of COVID-19 infection and hospitalization.

Methods

Setting and design

We conducted a retrospective, population-based cohort study within 3 regions of the Kaiser Permanente (KP) integrated health care delivery system: KP Colorado, KP Northwest, and KP Washington. Together, these regions serve about 2.1 million individuals who are generally representative of their region's population. As an integrated health care system, KP provides enrollees with both health care and insurance coverage. Care outside of KP is captured through insurance claims, resulting in near-complete capture of medication dispensing and health care utilization. KP regions maintain extensive electronic data on their members, including electronic clinical, pharmacy, and administrative data.[24]

Within these regions, we identified a cohort of eligible women 18 years of age or older. We used pharmacy dispensing data to define current exposure to exogenous estrogen-containing OCs or HT, laboratory results and diagnostic codes to identify women with COVID-19 infection, and hospitalization claims to identify COVID-19 hospitalization as a marker for severe disease. Study procedures were approved by the institutional review boards of KP Washington (reviewing on behalf of KP Northwest) and KP Colorado, with a waiver of consent.

Study population

Our study population included all women (identified by restricting to "females") at least 18 years of age with at least 6 months of health plan enrollment as of February 29, 2020. We excluded women for whom critical exposure and outcome data would routinely be missing, such as women living in geographic areas without a KP clinic. Analyses of OCs included women aged 18 to younger than 50 years who were not using HT. Analyses of hormone therapy included women aged at least 50 years who were not using OCs ($n = 323\,203$). Analyses of COVID-19 hospitalization were restricted to women with COVID-19 infection.

Current use of OCs and HT

From computerized pharmacy data, we identified all oral estrogens dispensed at KP or outside pharmacies and categorized them as OCs or HT. Pharmacy data included dispensing date, medication name and strength, number of pills dispensed, and estimated days' supply. We used the date of dispensing and days' supply to define the expected duration of a given dispensing, multiplying by 1.25 to account for imperfect adherence. We considered a person to be a "current user" for a given month if the first day of that month fell within the expected duration of a medication fill. We updated exposure variables monthly during follow-up. In COVID-19 infection analyses, COVID-19 infections during months defined by "current use" were considered to have occurred during "exposed" person-time. In COVID-19 hospitalization analyses, OC or HT use was defined at the start of the month in which the woman developed COVID-19 infection.

COVID-19 infection and hospitalization

COVID-19 infections were identified between March 1, 2020, and February 28, 2021, using laboratory results and inpatient diagnoses from within and outside KP. Laboratory results from many outside institutions were available via Epic's Care Everywhere feature, whereas diagnosis and utilization data from outside institutions came from insurance claims (expected to be complete because these are required for payment). COVID-19 infection was defined by (1) a positive polymerase chain reaction test result for SARS-CoV-2, or (2) hospitalization with an *International Classification of Diseases, 10th revision* (*ICD-10*), code for COVID-19 (codes B342, B9721, B9729, U071, U072, and J1282).

Among women with COVID-19 infections, we evaluated risk of hospitalization for COVID-19, which we defined by the earliest hospital admission date for (1) a hospitalization with an *ICD-10* diagnosis code for COVID-19, or (2) a hospitalization with a positive COVID-19 test result occurring from 28 days before the hospitalization through 3 days after hospital discharge. We reviewed a sample of charts from all sites to validate the COVID-19 hospitalization outcome. The positive predictive value for our definition of COVID-19 hospitalization was 96% ($n = 73$ or 76 charts; 95% CI, 89-99).[25]

Covariates

We identified demographic characteristics, including age in years, sex, and self-reported race and ethnicity from electronic health records. If ethnicity information was missing, we classified the individual as non-Hispanic (in part because, in some regions, "Hispanic" was offered as a response option within race instead of a separate question). We assessed socioeconomic status using the neighborhood deprivation index (NDI),[26] which draws on US census information; it is constructed using Z scores for variables such as neighborhood median household income and percentage of adults who have completed high school or completed college.[26] Higher values indicate more deprivation.

Electronic clinical data were used to define smoking status (current, former, and never; individuals missing smoking status were categorized as "never smoker"). Most recent body mass index (BMI) was calculated using clinical measures of weight (in kg) and height (in meters squared).

Comorbid conditions of interest were hypertension, history of myocardial infarction (MI), cerebrovascular disease, cancer, asthma, chronic obstructive pulmonary disease (COPD), and diabetes. These conditions were defined by the presence of at least 1 relevant *ICD-10* code (Table S1) at an ambulatory, emergency department, or inpatient encounter in the year prior to February 29, 2020. The Charlson comorbidity index, a general measure of health status,[27] was calculated on the basis of *ICD-10* codes from ambulatory, emergency department, and inpatient encounters in the past year. We used pharmacy dispensing data to identify current exposure to oral corticosteroids and anticoagulants at start of follow-up.

Statistical analysis

COVID-19 infection

We used weighted generalized estimating equation models[28,29] with the logit link to estimate odds ratios (ORs) and 95% CIs for the association between current OC or HT exposure (modeled as separate exposures in separate populations) updated monthly and COVID-19 infection. Within each month of follow-up, individuals were followed for COVID-19 infection; this was repeated for the full duration of follow-up. An unstructured covariance matrix was estimated to account for repeated measurements, and robust SE estimates were used to construct CIs and perform hypothesis tests.[29] We estimated a crude OR, an age-adjusted OR, and a fully adjusted OR (aOR), which adjusted for age (continuous), race, ethnicity, current smoking, KP region, NDI (tertiles), BMI (continuous), hypertension, history of MI, diabetes, cerebrovascular disease, cancer, current corticosteroid use, asthma, COPD, and calendar month.

COVID-19 hospitalization

Analyses of COVID-19 hospitalization were restricted to women with COVID-19 infection. We used logistic regression to estimate ORs and 95% CIs for the association between OC or HT exposure (defined by use at the start of the month of COVID-19 infection) and COVID-19 hospital admission. We estimated crude, age-adjusted, and fully adjusted models, including the same covariates as the COVID-19 infection models.

Missing data

We conducted complete case analyses for all models, excluding people with missing covariate data (for race, BMI, and NDI), and used stabilized, inverse probability weighting to account for the exclusion of these individuals.[30] Logistic regression models were used to estimate the probability of completeness of each covariate. Predictor variables in these models included age, Hispanic ethnicity, tobacco use, KP region, hypertension, history of MI, diabetes, cerebrovascular disease, cancer, oral corticosteroid use, asthma, COPD, Charlson comorbidity index score, OC or HT exposure status, and whether the person had 1 or more inpatient or outpatient visits within 1 year prior to cohort entry. For each model, predictor variables were dropped if they could not be estimated or if the predictor was causing large weights. Models for COVID-19 infection also incorporated stabilized follow-up weights for each month to account for potential differential loss to follow-up.[28,31] These follow-up models were estimated using logistic regression for each month of follow-up and were conditional on having follow-up in the prior month without a positive COVID infection outcome. These models included the same predictors as the probability of completeness models, in which the predictor was estimable and did not cause large weights. All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc.).

Results

Descriptive characteristics

Among our cohort of women younger than 50 years ($n = 306\,541$), 12.6% ($n = 38\,622$) were using an OC as of March 1, 2020 (Table 1). The mean age of the overall cohort was 34.2 years (SD 8.90). In general, current OC users were younger, slightly more likely to be White, slightly less likely to be of Hispanic ethnicity, and less likely to live in a neighborhood in the top tertile of deprivation. Users of OCs were also less likely to have a BMI greater than 30, less likely to have hypertension or diabetes, and more likely to have asthma than were nonusers (Table 1). Among women younger than 50 years, 221 898 (72.4%) had complete data for all covariates and were included in COVID-19 infection models.

Among women at least 50 years of age ($n = 323\,203$), 2.1% ($n = 6857$) were using HT as of March 1, 2020 (Table 1). The mean age of the overall cohort was 65.6 years (SD 10.15), and the most common chronic conditions were hypertension (33.4%), diabetes (18.5%), and asthma (9.8%) (Table 1). Compared with current nonusers of HT, current users were, on average, younger, more likely to be of White race, and slightly less likely to live in a neighborhood in the top tertile of deprivation. Current HT users also had a slightly lower mean BMI and were less likely to have hypertension, a history of MI, diabetes, cerebrovascular disease, or cancer and more likely to have asthma (Table 1). Among women aged 50 years or older, 285 221 (88.2%) had complete data for all covariates and were included in COVID-19 infection models.

COVID-19 infection

Among women not using OCs ($n = 267919$), COVID-19 infection occurred at a rate of 4.40 per 100 person-years and, among women using OCs ($n = 38\,622$), at a rate of 4.55 per 100 person-years (Table 2). There was no evidence of an association between current OC use and risk of COVID-19 infection (aOR = 1.05; 95% CI, 0.97-1.12) (Table 2; Figure 1).

Among women not using HT ($n = 316346$), COVID-19 infection occurred at a rate of 2.87 per 100 person-years and, among women using HT ($n = 6857$), at a rate of 3.22 per 100 person-years (Table 2). Current HT use was associated with a greater risk of COVID-19 infection than nonuse (aOR: 1.19; 95% CI, 1.03-1.38).

COVID-19 hospitalization

Among women younger than 50 years with COVID-19 infection ($n = 11\,727$), we identified 387 COVID-19 hospitalizations (3.8%) among nonusers of OC ($n = 10\,215$) and 25 COVID-19 hospitalizations (1.7%) among OC users ($n = 1512$) (Table 3; Figure 2). Women currently using OCs had a 39% lower risk of COVID-19 hospitalization than women not currently using OCs; this was of borderline statistical significance (aOR = 0.61; 95% CI, 0.38-1.0007).

Among eligible women aged 50 years or older with COVID-19, there were 1672 COVID-19 hospitalizations (19.8%) among women who were not currently using HT ($n = 8457$) and 19 COVID-19 hospitalizations (9.3%) among women currently using HT ($n = 204$) (Table 3; Figure 2). There was no evidence of an association between current HT use and COVID-19 hospitalization (aOR = 0.89; 95% CI, 0.51-1.53).

Discussion

In this population-based cohort study, there was no evidence of an association between current use of estrogen-containing OCs and COVID-19 infection. Current HT use was associated with a 19% greater risk of COVID-19 infection (95% CI, 3-38). Among

Table 1. Population characteristics by age group and current use of oral contraceptives and oral hormone therapy, United States, 2020.

Characteristic	Women < 50 years of age (n = 306 541)[a]		Women ≥ 50 years of age (n = 323 203)[a]	
	Current OC nonusers (n = 267 919)	Current OC users (n = 38 622)	Current HT nonusers (n = 316 346)	Current HT users (n = 6857)
KP region				
KPCO	81 221 (30.3)	13 917 (36.0)	105 786 (33.4)	2315 (33.8)
KPNW	109 643 (40.9)	13 953 (36.1)	111 085 (35.1)	2393 (34.9)
KPWA	77 055 (28.8)	10 752 (27.8)	99 475 (31.4)	2149 (31.3)
Age, mean (SD), years	34.8 (8.83)	30.5 (8.44)	65.6 (10.17)	62.8 (8.82)
Age range, years				
18-29	82 246 (30.7)	19 803 (51.3)		
30-39	92 905 (34.7)	11 825 (30.6)		
40-49	92 768 (34.6)	6994 (18.1)		
50-59			100 894 (31.9)	2916 (42.5)
60-69			108 573 (34.3)	2374 (34.6)
70-79			72 603 (23.0)	1223 (17.8)
80-89			27 278 (8.6)	297 (4.3)
≥ 90			6998 (2.2)	47 (0.7)
Race[b]				
Asian	22 478 (10.2)	2675 (7.8)	18 957 (6.5)	114 (1.7)
Black	11 952 (5.4)	1068 (3.1)	10 438 (3.6)	136 (2.1)
NH/PI or IA/AN	3787 (1.7)	393 (1.1)	2918 (1.0)	51 (0.8)
Mixed race or other	14 474 (6.6)	2127 (6.2)	11 886 (4.1)	217 (3.3)
White	167 121 (76.0)	28 058 (81.8)	248 132 (84.9)	6052 (92.1)
Missing data	48 107 (18.0)	4301 (11.1)	24 015 (7.6)	287 (4.2)
Ethnicity				
Hispanic	32 552 (12.1)	3925 (10.2)	23 365 (7.4)	361 (5.3)
Non-Hispanic	235 367 (87.9)	34 697 (89.8)	292 981 (92.6)	6496 (94.7)
Duration of KP enrollment, mean (SD), years	4.9 (5.39)	5.8 (6.01)	10.6 (9.12)	10.5 (8.77)
Neighborhood deprivation index tertile,[b,c]				
Lowest	83 900 (31.5)	14 062 (36.7)	107 793 (34.3)	2639 (38.8)
Middle	87 221 (32.8)	12 540 (32.7)	106 611 (33.9)	2283 (33.5)
Highest	94 959 (35.7)	11 742 (30.6)	100 180 (31.8)	1888 (27.7)
Charlson Comorbidity Score				
0	231 970 (86.6)	33 419 (86.5)	189 724 (60.0)	4533 (66.1)
1	29 348 (11.0)	4727 (12.2)	52 511 (16.6)	1334 (19.5)
≥ 2	6601 (2.5)	476 (1.2)	74 111 (23.4)	990 (14.4)
BMI, mean (SD), kg/m^2[b]	28.9 (7.81)	27.7 (7.17)	29.2 (7.14)	27.8 (6.02)
BMI[b]				
< 18.5	3500 (1.6)	602 (1.8)	4807 (1.6)	106 (1.6)
18.5-24.9	79 873 (36.0)	14 225 (42.6)	89 487 (30.1)	2389 (35.7)
25.0-29.9	58 836 (26.5)	8933 (26.8)	89 837 (30.2)	2202 (32.9)
30.0-34.9	37 005 (16.7)	4766 (14.3)	58 724 (19.7)	1217 (18.2)
35.0-39.9	21 498 (9.7)	2483 (7.4)	30 713 (10.3)	512 (7.6)
≥ 40.0	20 924 (9.4)	2351 (7.0)	23 876 (8.0)	273 (4.1)
Current smoker	15 848 (5.9)	1283 (3.3)	18 340 (5.8)	311 (4.5)
Hypertension	13 095 (4.9)	1118 (2.9)	106 163 (33.6)	1899 (27.7)
History of MI	305 (0.1)	10 (0.0)	6989 (2.2)	83 (1.2)
Diabetes	15 865 (5.9)	1637 (4.2)	59 110 (18.7)	738 (10.8)
Cerebrovascular disease	565 (0.2)	27 (0.1)	10 847 (3.4)	112 (1.6)
Cancer in the past 2 years	2257 (0.8)	157 (0.4)	16 286 (5.1)	174 (2.5)
Asthma	22 744 (8.5)	3907 (10.1)	30 643 (9.7)	913 (13.3)
COPD	458 (0.2)	28 (0.1)	15 265 (4.8)	241 (3.5)
Anticoagulant use	226 (0.1)	8 (0.0)	5340 (1.7)	69 (1.0)
Oral corticosteroid use	1165 (0.4)	161 (0.4)	4382 (1.4)	125 (1.8)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HT, hormone therapy; IA/AN, Indigenous American/Alaskan Native; KP, Kaiser Permanente; KPCO, Kaiser Permanente Colorado; KPNW, Kaiser Permanente Northwest; KPWA, Kaiser Permanente Washington; MI, myocardial infarction; NH/PI, Native Hawaiian/Pacific Islander; OC, oral contraceptive.
[a]Data are reported as no. (%) unless otherwise indicated.
[b]Percentages reported are of nonmissing values. Characteristics with missing values, by total population < 50 years and total population ≥ 50 years: BMI (calculated as weight in kilograms divided by height in meters squared: < 50 years = 16.8%; ≥ 50 years = 5.9%); neighborhood deprivation index (< 50 years = 0.7%; ≥ 50 years = 0.6%); race (< 50 years = 17.1%; ≥ 50 years = 7.5%).
[c]Higher values indicate more neighborhood deprivation.

women with COVID-19 infection, women currently using OCs had a 39% lower risk of COVID-19 hospitalization (95% CI, 0-62). There was no evidence of an association of HT use with COVID-19 hospitalization. These findings suggest that, at a minimum,

Table 2. Association of current oral contraceptive use among women < 50 years and hormone therapy use among women ≥ 50 years and risk of COVID-19 infection, United States, 2020-2021.

	Person-years[a]	No. of events (COVID-19 infection)[a]	Crude event rate (per 100 person-years)[a]	Crude OR (95% CI)[b]	Age-adjusted OR (95% CI)[b]	Fully adjusted OR (95% CI)[b,c]
Current OC use status						
Nonuse	231 980	10 215	4.40	Referent	Referent	Referent
Use	33 257	1512	4.55	1.03 (0.98-1.09)	1.00 (0.95-1.06)	1.05 (0.97-1.12)
Current HT use status						
Nonuse	294 207	8457	2.87	Referent	Referent	Referent
Use	6326	204	3.22	1.13 (0.98-1.29)	1.07 (0.93-1.22)	1.19 (1.03-1.38)

Abbreviations: HT, hormone therapy; OC, oral contraceptive; OR, odds ratio.
[a]Person-years, no. of events, and crude event rate estimated within total eligible population, as presented in Table 1. For analyses among women < 50 years, $n = 306\,541$ (OC nonusers, $n = 267\,919$; OC users, $n = 38\,622$); for analyses among women ≥ 50 years, $n = 323\,203$ (HT nonusers $n = 316\,346$; HT users $n = 6857$).
[b]All analyses were conducted as complete case analyses, excluding people with missing covariate data. In models among women < 50 years, $n = 221\,898$ complete cases; in models among women ≥ 50 years, $n = 285\,221$ complete cases.
[c]Adjusted for continuous age, race, ethnicity, smoking, site, neighborhood deprivation index, continuous body mass index, hypertension, history of myocardial infarction, diabetes, cerebrovascular disease, cancer, current corticosteroid use, asthma, chronic obstructive pulmonary disease, and calendar month.

current OC and HT use do not meaningfully increase the risk of either COVID-19 infection or hospitalization.

To our knowledge, this is the first US-based study of estrogen-containing OCs or HT in relation to COVID-19 infection, and the third such study worldwide.[22,23] Prior studies have had inconsistent results and, of importance, numerous methodological differences make a direct comparison between our study and previously published results difficult.[22,23] Previous studies relied on self-reported information about medication exposure[22,23] and self-reported COVID-19 outcomes,[22] were conducted when SARS-CoV-2 testing was not widely available,[22,23] and relied on populations of self-selected volunteers.[22,23]

Although a direct comparison between our results and those of published studies is difficult due to these methodologic differences, findings from these prior studies may assist in contextualizing our results. In a UK-based cohort study with data from March–June 2020, self-reported current OC use was associated with 13% lower risk of "predicted COVID-19" (defined based on symptoms; aOR = 0.87; 95% CI, 0.81-0.93),[22] whereas self-reported current HT use was associated with 32% greater risk of "predicted COVID-19" (aOR = 1.32; 95% CI, 1.16-1.49).[22] In an Italian survey-based study, there was no evidence of an association between current or recent OC or HT use (OC vs HT not differentiated) among women aged 18 years or older (mean age, 48 years) and a self-reported positive SARS-CoV-2 test (aOR = 0.95; 95% CI, 0.81-1.10).[23] A secondary analysis found that current or recent exogenous hormone use among women at least 60 years of age (likely to be using HT rather than OCs) was associated with a 46% lower risk of a positive SARS-CoV-2 result than never-use of exogenous hormones (aOR = 0.54; 95% CI, 0.36-0.80).[23] Therefore, the lack of an association between OC use and COVID-19 infection in our study was inconsistent with the lower risk of predicted COVID-19 reported in the UK-based study[22] but consistent with results from the Italian study.[23] Our finding for current HT use was consistent with the greater risk of predicted COVID-19 reported in the UK-based study[22] but inconsistent with the finding

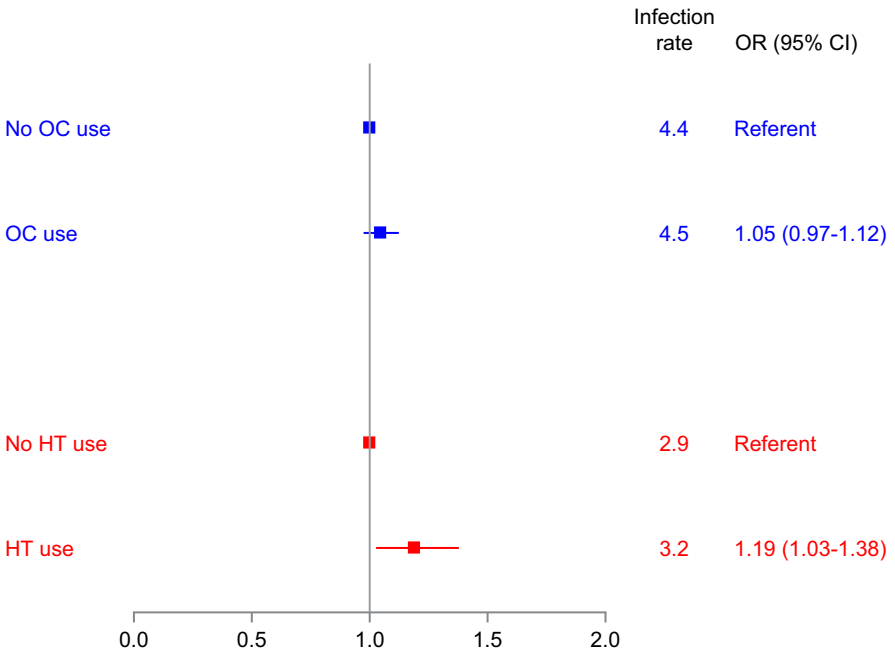

Figure 1. Association of current oral contraceptive (OC) use and hormone therapy (HT) use and risk of coronavirus disease 2019 (COVID-19) infection, United States, 2020-2021. Infection rate is reported per 100 person-years. OR, odds ratio.

Table 3. Among women diagnosed with COVID-19, association of oral contraceptive use among women < 50 years and hormone therapy use among women ≥ 50 years and risk of COVID-19 hospitalization, United States, 2020-2021.

	No.	No. of events (COVID-19 hospitalization)	Hospitalized, %	Crude OR (95% CI)[a]	Age-adjusted OR (95% CI)[a]	Fully adjusted OR (95% CI)[a,b]
Current OC use status						
Nonuse	10215	387	3.8	Referent	Referent	Referent
Use	1512	25	1.7	0.43 (0.28-0.64)	0.48 (0.32-0.73)	0.61 (0.38-1.00)[c]
Current HT use status						
Nonuse	8457	1672	19.8	Referent	Referent	Referent
Use	204	19	9.3	0.42 (0.26-0.67)	0.58 (0.35-0.94)	0.89 (0.51-1.53)

Abbreviations: HT, hormone therapy; OC, oral contraceptive; OR, odds ratio.
[a]All analyses were conducted as complete cases analyses, excluding people with missing covariate data. In models among women < 50 years, $n = 7882$ complete cases; in models among women ≥ 50 years, $n = 7348$ complete cases.
[b]Adjusted for continuous age, race, ethnicity, smoking, site, neighborhood deprivation index, continuous body mass index, hypertension, history of myocardial infarction, diabetes, cerebrovascular disease, cancer, oral corticosteroid use, asthma, chronic obstructive pulmonary disease, month of COVID infection.
[c]Without rounding, upper limit of CI = 1.0007.

of reduced risk for women age 60 years or older in the Italian study.[23]

Our finding that women currently using estrogen-containing OCs had a 39% lower risk of COVID-19 hospitalization was consistent with the lower risk of COVID-19 hospitalization reported in the UK-based study (OR = 0.79; 95% CI, 0.64-0.97).[22] As in our study, the UK-based study found no evidence that current HT use was associated with risk of COVID-19 hospitalization. In the Italian study, there was no evidence that current or recent use of any exogenous hormone (OC vs HT was not differentiated) was associated with risk of severe infection (defined as COVID-19 hospitalization or pneumonia).[23] Several studies have evaluated death rather than hospitalization as the severe outcome of interest[32-34] and consistently found that current use of oral HT was associated with a decreased risk of death (aOR range, 0.22 [95% CI, 0.05-0.94][32] to 0.47 [95% CI, 0.34-0.63][34]). Current use of estrogen-containing OCs was evaluated in only 1 of these studies, with no evidence of an association with risk of death (aOR = 1.0; 95% CI, 0.41-2.4).[33] Although these studies suggest a protective role of current HT use in relation to a severe COVID outcome (death),[32-34] they are not directly comparable to our study's evaluation of COVID hospitalization due to the difference in severity of the outcomes and the time period studied.[32-34]

Strengths and limitations

Strengths of this study include the use of rich electronic health record data from integrated health care systems in 3 geographic regions. These health care systems are generally representative of their region's population. Members receive most of their care within KP, and outside care data are captured via claims, resulting in nearly complete capture of exposure and outcomes. We were able to study both outpatient and hospitalized cases as outcomes. Time-varying OC and HT use exposure was defined using prescription dispensing data, rather than self-report.[22,23] Use of prescription dispensing data is the gold standard in pharmacoepidemiologic research and likely more accurately represents current exposure to OC and HT than does self-reported

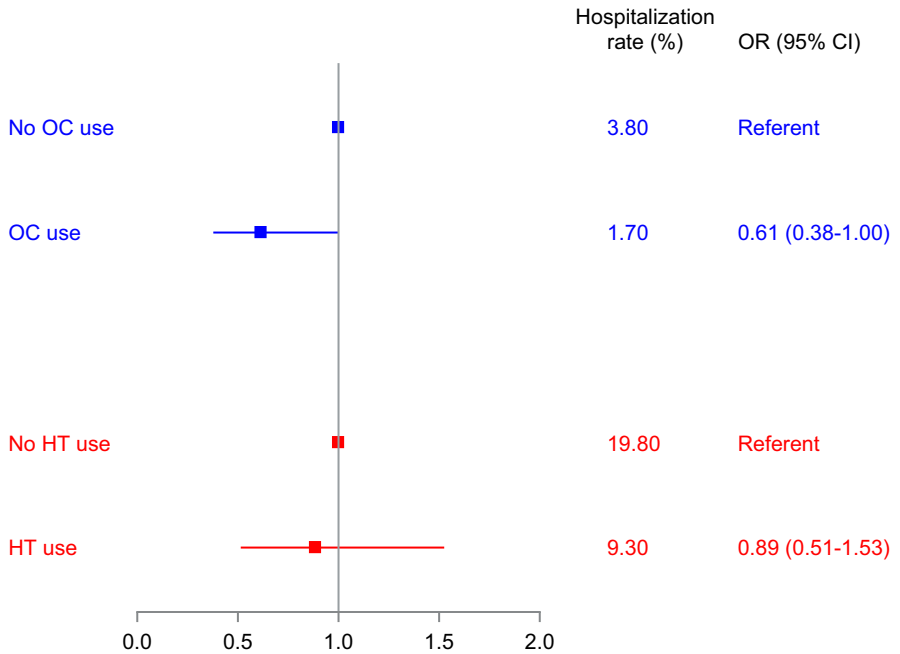

Figure 2. Among women with coronavirus disease 2019 (COVID-19), association between current oral contraceptive (OC) use and hormone therapy (HT) use and risk of COVID-19 hospitalization, United States, 2020-2021. OR, odds ratio.

medication use. In contrast to prior studies that relied on self-reported COVID-19 outcomes,[22] our population-based study defined COVID-19 outcomes via testing results and diagnosis codes. Self-reported outcomes included in prior studies are likely underreported, which may bias findings.

As limitations, we cannot rule out residual confounding by indication; however, we were able to adjust for numerous potential confounders identified a priori, including demographic characteristics and comorbid conditions. Current users of OCs or HT may have been healthier than nonusers. Although there is the potential for differences in associations by OC or HT type (estrogen-containing vs progestin-only for OCs; estrogen-only vs estrogen plus progestin for HT) or estrogen and progestin dose, we would be unable to make meaningful conclusions within these subpopulations of users due to sample size; thus, an evaluation of OC and HT type or dose was outside of our study's scope. As an additional limitation, we did not attempt to identify pregnancies occurring in our cohort, and thus we did not censor person-time occurring during pregnancy. We expect that all or almost all of this person-time would be included in the OC nonuse category. Given that pregnancy is also associated with a unique endogenous hormonal milieu, there may be some person-time contributed by pregnant women to the category of current OC nonuse that included comparatively high levels of endogenous estrogens. We recognize that the combination of pregnant and nonpregnant women not currently using OCs may result in a heterogeneous group in regard to endogenous estrogen levels. It is not known in what way high levels of endogenous estrogen might modify the risk of COVID-19 infection or hospitalization. If we assume that the inclusion of some pregnant person-time in the category of OC nonuse has the potential to artificially elevate exposure to estrogen in this group, we conjecture this could have biased our results toward the null. Furthermore, our identification of "women" eligible for this study has potential for some misclassification because sex was defined using the integrated health system's binary classification of "male" and "female," with gender identity data currently unavailable. COVID-19 infection and hospitalization risk may be differently associated with exogenous hormone use among populations of transgender persons.

Also as limitations, COVID-19 testing was difficult to access early in the pandemic and accessibility changed throughout the pandemic, which likely resulted in missed COVID-19 infections. These limitations are not unique to our study but are byproducts of inconsistent testing done throughout the COVID-19 pandemic. However, with follow-up through February 2021, ours is the only study of the 3 (ie, ours and the 2 European studies[22,23]) with follow-up past June 2020, thus encompassing the period when SARS-CoV-2 testing via nucleic acid amplification tests was available widely but not yet commonly replaced by at-home rapid antigen tests, which became widely available in the United States in 2022. The period encompassed by our study reduces the likelihood of missing COVID-19 infections identified by at-home rapid tests that were not reported to the health care system. Findings of prior studies using self-reported outcome data and conducted when SARS-CoV-2 testing was not widely available[22,23] were likely affected by selective testing and misclassified outcomes, which could bias results in either direction.

Conclusion

The findings of our study suggest that neither current OC nor HT use is associated with a meaningfully greater risk of either COVID-19 infection or hospitalization. This should provide some reassurance to women and their physicians. Indeed, use of an OC was associated with a moderately lower risk of COVID-19 hospitalization among women infected with COVID-19, supporting the hypotheses that exogenous OC use may be associated with a reduced risk of severe COVID-19 outcomes.

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Supplementary material

Supplementary material is available at *the American Journal of Epidemiology* online.

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Conflict of interest

S.P.F. has a research contract from Pfizer BioNTech as a site for clinical trials of their SARS-CoV-2 RNA vaccine, which is unrelated to the work reported in this article. L.A.T. and S.D. have received research funding on an unrelated topic from GlaxoSmithKline; S.D. has received funding from Jazz Pharmaceuticals for unrelated work; and J.K. has research contracts with Vir Biotechnology and Pfizer, both unrelated to this work. The other authors declare no conflicts.

Disclaimer

Sponsors had no role in the study design; collection, analysis, and interpretation of data; the writing of the report, or in the decision to submit the article for publication.

Data availability

Study participants did not give written consent for their data to be shared publicly, and the data contain protected health information governed by the US Health Insurance Portability and Accountability Act. For these reasons, we do not plan to share data publicly, but the authors will respond to reasonable requests, with permission of all health systems involved and a fully executed data use agreement.

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