Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users

Stephen Sidneya,⁎, T. Craig Cheethamb, Frederick A. Connellc, Rita Ouellet-Hellstromd, David J. Grahamd, Daniel Davisd, Michael Sorela, Charles P. Quesenberry, Jr.a, William O. Coopere

aDivision of Research, Kaiser Permanente Northern California, Oakland, CA 94612, USA
bPharmacy Analytical Services, Kaiser Permanente Southern California, Downey, CA, USA
cUniversity of Washington, School of Public Health, Seattle, WA, USA
dFDA Office of Surveillance and Epidemiology, Silver Spring, MD, USA
eDepartment of Pediatrics, Vanderbilt University, Nashville, TN, USA

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Abstract

Background: Combined hormonal contraceptives (CHCs) place women at increased risk of venous thromboembolic events (VTEs) and arterial thrombotic events (ATEs), including acute myocardial infarction and ischemic stroke. There is concern that three recent CHC preparations [drospirenone-containing pills (DRSPs), the norelgestromin-containing transdermal patch (NGMN) and the etonogestrel vaginal ring (ETON)] may place women at even higher risk of thrombosis than other older low-dose CHCs with a known safety profile.

Study Design: All VTEs and all hospitalized ATEs were identified in women, ages 10–55 years, from two integrated health care programs and two state Medicaid programs during the time period covering their new use of DRSP, NGMN, ETON or one of four low-dose estrogen comparator CHCs. The relative risk of thrombotic and thromboembolic outcomes associated with the newer CHCs in relation to the comparators was assessed with Cox proportional hazards regression models adjusting for age, site and year of entry into the study.

Results: The hazards ratio for DRSP in relation to low-dose estrogen comparators among new users was 1.77 (95% confidence interval 1.33–2.35) for VTE and 2.01 (1.06–3.81) for ATE. The increased risk of DRSP was limited to the 10–34-year age group for VTE and the 35–55-year group for ATE. Use of the NGMN patch and ETON vaginal ring was not associated with increased risk of either thromboembolic or thrombotic outcomes.

Conclusions: In new users, DRSP was associated with higher risk of thrombotic events (VTE and ATE) relative to low-dose estrogen comparator CHCs, while the use of the NGMN patch and ETON vaginal ring was not.

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1. Introduction

It is well known that the use of combined hormonal contraceptives (CHCs) is associated with an increased risk of venous thromboembolic events (VTEs), including deep vein thrombosis (DVT) and pulmonary embolism (PE), and may be associated with an increased risk of the arterial thromboembolic events (ATEs), including acute myocardial infarction (AMI) and ischemic stroke (IS) [1–3]. During the past 10 years, three new CHC preparations have been approved for use by the US Food and Drug Administration (FDA), including drospirenone/ethinyl estradiol pills (DRSPs), norelgestromin/ethinyl estradiol transdermal patch (NGMN) and the etonogestrel/ethinyl estradiol vaginal ring (ETON).

Since marketing of these three new preparations began, there have been several studies evaluating the risk of thrombotic and thromboembolic events for two of them (DRSP and NGMN) compared to low-dose estrogen CHCs...
that have been on the market for longer periods of time. The results have been mixed, with five out of eight studies showing an increased risk of VTE with DRSP [4–12] and two of five showing an increased risk with NGMN [13–19]. It is unclear whether the differences in findings arose from differences in study methodologies or differences in the populations studied. A recently published study showed a modest increase of VTE risk with the ETON vaginal ring [19]. Only four studies have examined the risk of ATEs with any of these preparations, and none have shown significant associations [4,12,17,20].

Thus, there is a great deal of concern and confusion among women and their health care providers regarding the safety of these newer preparations relative to older CHCs. We therefore performed this study to address methodological issues using a new user design [21] to assess the risk of each of the three newer CHCs relative to low-dose estrogen CHCs in a cohort of more than 573,000 new users of CHCs from four geographically and demographically diverse health plans.

Materials and methods

2.1. Study sites

Study sites included Kaiser Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), Vanderbilt University (Tennessee State Medicaid) and University of Washington (Washington State Medicaid). Computerized data files were used to obtain enrollment data, demographic information, ambulatory prescriptions from pharmacy records or claims, hospitalization and outpatient visit data with diagnoses from health plan records or claims, and mortality obtained from state mortality files.

The study was approved by the institutional review board at each participating institution.

2.2. Study and comparator CHCs

The study CHCs included the following: drospirenone (3.0 mg)/ethinyl estradiol (30 mcg) tablets (DRSP), the norelgestromin (6.0 mg)/ethinyl estradiol (750 mcg) transdermal patch (NGMN) and the etonogestrel (11.7 mg)/ethinyl estradiol (2700 mcg) vaginal ring (ETON). The comparator CHCs included the following low-dose estrogen CHCs: levonorgestrel (0.10 mg)/ethinyl estradiol (20 mcg) tablets (LNG10-20), levonorgestrel (0.15 mg)/ethinyl estradiol (30 mcg) tablets (LNG15-30), norethindrone (1 mg)/ethinyl estradiol (20 mcg) tablets (NETA) and norgestimate (0.18–0.25 mg)/ethinyl estradiol (35 mcg) tablets (NGM).

2.3. Study population

We identified 860,087 women, ages 10–55 years, who had at least one prescription for a study CHC or comparator CHC between January 1, 2001, and December 31, 2007, which was also preceded by at least 6 months of continuous membership. We excluded 12,704 women with claims evidence of severe life-threatening disease (sickle cell disease, cystic fibrosis, cerebral palsy, cancer, HIV, organ transplant, liver failure, severe congestive heart failure, renal failure, respiratory failure) or evidence of a study endpoint: outpatient DVT or hospitalized VTE or ATE (AMI or IS) in the 6 months before study entry. We additionally excluded 9227 women whose only CHC exposures occurred during periods of pregnancy and 2330 women whose only CHC prescription(s) was for two or more CHCs on the same date. The final cohort included 835,826 women.

From this cohort, we identified new users, defined as first exposure to any study CHC or comparator CHC during the 2001–2007 study period and no previous use of any CHC — study, comparator or non-study CHC — during the study period. Additionally, women whose first exposure to a study or comparator CHC occurred during the first 6 months of 2001 were required to have no previous use of any CHC during the 6 months preceding cohort entry. We identified 573,680 new users; these women had a total of 367,138 person-years of exposure.

2.4. Exposure periods

Exposure periods were calculated using the fill date of the CHC prescription. If a second prescription for the same CHC was filled during the time period of the first prescription, then the start date of the second prescription was adjusted to correspond to the day after the first prescription ended. This procedure was repeated until the time period covered by successive prescriptions with the first CHC ended or until a prescription for a second CHC was filled, thereby ending the exposure period to the first CHC. To reduce misclassification, we identified a period of indeterminate use, defined as the 42-day period of time immediately after a prescription period ended, to account for any persisting physiological effects of CHCs on cardiovascular risk (i.e., increased coagulability). Since only 15% of person-time and 16% of the endpoints occurred during periods of “indeterminate use,” we did not analyze this group separately and included the person-time and endpoints in our analysis of new users.

2.5. Follow-up

Follow-up was evaluated independently for each of the study outcomes. End of follow-up for each woman in the new user cohort was defined as the first of the following dates: end of exposure to the study entry CHC or comparator, last date of continuous membership, development of study endpoint, end of study follow-up (12/31/2007) or date of 56th birthday.

2.6. Pregnancy

Because of the known hypercoagulability associated with pregnancy, periods of pregnancy were estimated by identifying claims for terminations and deliveries. For each abortion, we estimated the period of pregnancy to include
120 days prior to the date of the abortion, and we also excluded CHC exposures and events occurring within 42 days after the abortion. For each delivery, we estimated the period of pregnancy to include 270 days prior to the date of the delivery, and we also excluded CHC exposure and events occurring within 42 days after the delivery. The pregnancy exclusion resulted in the exclusion of four potential study endpoints and a small amount of potential exposure time (0.6%).

2.7. Study endpoints

The primary study endpoints were as follows: hospitalized ATE (including AMI and IS), hospitalized and outpatient VTEs, and total mortality. All potential hospitalized cases were identified by the sites using the primary discharge codes: AMI (410.x), IS (430, 431, 432.0, 432.9, 433.x, 434.x, 436) and VTE (PE code 415.1 and DVT codes 451.1, 451.1x, 451.2, 451.8, 451.81, 451.82, 451.84, 451.89, 453.0, 453.1, 453.2, 453.3, 453.4, 453.8, 453.9). Outpatient DVT was identified by a diagnosis of DVT in conjunction with a first prescription for an anticoagulant during the 30-day period subsequent to the date of diagnosis. Mortality was assessed by linkage of membership data to state mortality files.

Medical records were requested on all potential hospitalized endpoints. The key elements of the hospitalization medical record (e.g., admission and discharge summaries, laboratory tests, imaging study results) were deidentified and sent to the study lead site (KPNC) for adjudication. Physician adjudicators (a cardiologist, neurologist and two other physicians) blinded to the case exposure status applied case definitions based on clinical diagnosis of the study endpoints utilizing clinical data about the patient, plus electrocardiogram and biomarker (blood creatine kinase-MB, troponin) findings for AMI and imaging study findings for stroke (e.g., brain computed tomography or magnetic resonance imaging) and VTE (e.g., Doppler exam, ventilation–perfusion scan, pulmonary angiography). Potential stroke and VTE cases for which imaging studies were not performed or findings were unavailable were excluded from the analysis. Cases for which the adjudication decision was ambiguous were discussed and resolved with the lead principal investigator.

We obtained 874 of 947 (92.3%) medical records for potential hospitalization endpoints, of which 377 were medical records of new users (34 AMIs, 90 strokes, 253 VTEs). We excluded the 73 potential cases for which medical records were not available from the analytic data set. In new users, 221 of the 253 (87.4%) potential cases reviewed were validated as true VTEs, and 28 of the 34 AMIs (82.4%) reviewed were validated as true AMIs. Of the 90 potential stroke cases reviewed, 55 (61.1%) were validated as true stroke syndromes, of which 37 were ischemic strokes (68.7%) (18 were of nonatherothrombotic etiology). Of the 35 cases that did not meet the criteria of cause (brain trauma, tumor, infection). Records of outpatient DVTs were obtained from one of the sites (KPNC) and were adjudicated by the lead principal investigator. Of the 48 adjudicated outpatient DVTs in new users, 40 met the criteria for definite or probable VTE (83.3% positive predictive value). Validation of outpatient DVT was not possible at the Medicaid sites because the outpatient medical records were unavailable and validation was not performed at KPSC. Given the 83% validation rate for outpatient DVT at the KPNC site, we chose to include all 60 outpatient DVT cases from the three other sites in the final analysis.

2.8. Covariates

Predefined covariates that were potential confounders or effect modifiers were ascertained from the electronic databases and were included if they were present in 1% or more of the cohort. For the new user analysis, medical conditions were considered to be present from the first date they were identified, whether during the exposure period or during the 6 months prior to the exposure. Medications during periods of CHC use were considered as time-dependent covariates based on prescription lengths and fill dates. Hospitalizations for surgery or injury were evaluated as time-dependent covariates. To account for hypercoagulability following surgery and injury, we included a period of 6 weeks following the event as a time-dependent covariate.

2.9. Statistical approach

Age-adjusted incidence rates were also calculated using direct adjustment with the age distribution of the entire study population at cohort entry as the standard. All data analyses were performed using SAS 9.2.

Cox proportional hazards regression was used to estimate the relative risk of study endpoints associated with current use of each study CHC relative to comparator CHCs. CHC exposure was considered as a four-level covariate, capturing current use of each of the three study CHCs with the four comparators combined as one category. We also performed the analyses using LNG15-30 alone as the comparator and report the major findings for these analyses since LNG15-30 is the only one of the four comparators that has the same ethinyl estradiol content (30 mcg) as the study CHC, DRSP. Time since cohort entry was the time scale in the models. Cox regression models were stratified on age, allowing for separate baseline hazards for each age category (5-year intervals); additional control for potential residual confounding within age strata was achieved via inclusion of age as a continuous covariate in the regression model. Age (continuous), site and calendar year of entry into study were included in all models. Established risk factors (hypertension, hyperlipidemia and diabetes mellitus) were included as fixed covariates in the ATE models. Each of the other potential covariates was tested individually in these base models, with a decision to include it in further model testing if the estimate of relative risk was associated with any of the
study CHCs was changed by 10% or more. None of the covariates met this criterion for any of the models, so none were included in the final modeling.

3. Results

The final study cohort of the new CHC users included 573,680 women. More than three quarters (78%) were 15–34 years of age (Table 1). The mean age of new users was 26.4 years at initiation of use, ranging from 23.4 years for users of the NGMN patch to 27.2 years for users of the comparator group. There were site differences in the use of new CHCs, most notably that the NGMN was the most commonly used study contraceptive at the Medicaid sites.

The prevalence of covariates by CHC is shown in Table 2. The prevalence of most of the covariates associated with the study CHCs was lower than or similar to the prevalence in users of comparator CHCs except for acne (4% for DRSP new users vs. 2% for comparators).

The overall crude incidence of the study endpoints was 1.77 per 10,000 person-years for ATE and 8.74 per 10,000 person-years for VTE.

### Table 1
New users: study and comparator CHC users by age and site (column percents)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DRSP</th>
<th>NGMN</th>
<th>ETON</th>
<th>Comparators</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–14</td>
<td>3000</td>
<td>2429</td>
<td>126</td>
<td>11,260</td>
<td>16,815</td>
</tr>
<tr>
<td>15–24</td>
<td>35,792</td>
<td>17,549</td>
<td>7105</td>
<td>114,061</td>
<td>174,507</td>
</tr>
<tr>
<td>25–34</td>
<td>13,110</td>
<td>448</td>
<td>712</td>
<td>59,556</td>
<td>79,109</td>
</tr>
<tr>
<td>35–44</td>
<td>2684</td>
<td>48</td>
<td>260</td>
<td>4,214</td>
<td>5,194</td>
</tr>
<tr>
<td>45–55</td>
<td>109,070</td>
<td>62,316</td>
<td>19,143</td>
<td>383,151</td>
<td>573,680</td>
</tr>
</tbody>
</table>

Site

<table>
<thead>
<tr>
<th>Site</th>
<th>N</th>
<th>N</th>
<th>N</th>
<th>N</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPNC</td>
<td>51,081</td>
<td>6968</td>
<td>2974</td>
<td>152,734</td>
<td>213,487</td>
</tr>
<tr>
<td>KPSC</td>
<td>43,971</td>
<td>15,393</td>
<td>8217</td>
<td>134,586</td>
<td>202,167</td>
</tr>
<tr>
<td>Vanderbilt</td>
<td>9849</td>
<td>20,755</td>
<td>3917</td>
<td>65,714</td>
<td>100,235</td>
</tr>
<tr>
<td>Washington</td>
<td>4169</td>
<td>19,470</td>
<td>4035</td>
<td>30,117</td>
<td>57,791</td>
</tr>
<tr>
<td>Total</td>
<td>109,070</td>
<td>62,316</td>
<td>19,143</td>
<td>383,151</td>
<td>573,680</td>
</tr>
</tbody>
</table>

Study CHCs: DRSP, NGMN and ETON.
Comparators: LNG10-20, LNG15-30, NETA and NGM.

### Table 2
Distribution of covariates: study CHC in new users for combined sites

<table>
<thead>
<tr>
<th>Covariate</th>
<th>DRSP N=109,070</th>
<th>NGMN N=62,316</th>
<th>ETON N=19,143</th>
<th>Comparators N=383,151</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>927</td>
<td>418</td>
<td>185</td>
<td>5312</td>
</tr>
<tr>
<td>Acne</td>
<td>4606</td>
<td>420</td>
<td>157</td>
<td>8203</td>
</tr>
<tr>
<td>Asthma</td>
<td>3273</td>
<td>1930</td>
<td>642</td>
<td>10,924</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1639</td>
<td>834</td>
<td>314</td>
<td>8052</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2151</td>
<td>1245</td>
<td>387</td>
<td>7621</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>3952</td>
<td>3838</td>
<td>839</td>
<td>20,389</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1889</td>
<td>934</td>
<td>328</td>
<td>8750</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2625</td>
<td>1368</td>
<td>557</td>
<td>14,335</td>
</tr>
<tr>
<td>Migraine</td>
<td>2117</td>
<td>1328</td>
<td>478</td>
<td>7423</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>19,752</td>
<td>12,657</td>
<td>3307</td>
<td>78,028</td>
</tr>
<tr>
<td>Statins</td>
<td>763</td>
<td>315</td>
<td>123</td>
<td>4065</td>
</tr>
<tr>
<td>Surgery or Injury</td>
<td>1000</td>
<td>315</td>
<td>153</td>
<td>4904</td>
</tr>
</tbody>
</table>

Covariates selected because they each had a prevalence of at least 1% in at least one of the CHC categories.
ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs; NS, not significant.

p value of $\chi^2$ test for percentage of covariate for each exposure CHC with percentage of covariate for comparator group:
*p value<.01.
**p value<.001.
Percent refers to new users of study CHC.
Study CHCs: DRSP, NGMN and ETON.
Comparators: LNG10-20, LNG15-30, NETA and NGM.
adjusted incidence rates of hospitalized ATE, all VTEs and total mortality are shown in Table 3. As expected, the incidence rates for ATE and VTE increased with age, with 57% of ATE and VTEs occurring in the 35–55-year age group even though only 23% of the follow-up time was in this group.

The relative hazards of study endpoints associated with new use of the study CHCs in relation to the combined comparators are shown in Table 4. New use of DRSP was associated with increased risk of VTE [relative hazard (HR) 1.77, 95% confidence interval (CI) 1.33–2.35] and ATE (HR 2.01, 1.06–3.81) when compared to all comparators. The increased risk of VTE in new users was restricted to women, ages 10–34 years (HR 2.12, 1.43–3.15), while the increased risk of ATE was restricted to women, ages 35–55 years (HR 2.60, 1.25–5.41). In secondary analyses, the DRSP risk estimates were elevated for outpatient DVT (HR 1.51, 1.00–2.28), hospitalized DVT (HR 1.74, 1.00–3.02), all DVT (HR 1.58, 1.09–2.28), hospitalized PE (HR 2.22, 1.41–3.36) and all hospitalized VTE (HR 2.08, 1.46–2.98). NGMN and ETON were not associated with an increased risk for any of the study endpoints.

When comparing DRSP with LNG15-30 alone (137,311 new LNG15-30 users), the relative risk was similar for all VTE (HR 1.57, 1.13–2.18) and was not statistically increased for ATE (HR 1.64, 0.79–3.40), while the age-specific findings of increased risk of VTE in DRSP new users 10–
Table 5
Age- and site-adjusted incidence rates for hospitalized ATEs, all VTEs and all-cause mortality by study contraceptive type and duration of use among new users (rates per 10,000 person-years, 95% CI in parentheses)

<table>
<thead>
<tr>
<th>CHC/duration of use</th>
<th>ATE Events (N)</th>
<th>Rate</th>
<th>VTE Events (N)</th>
<th>Rate</th>
<th>Total mortality Events (N)</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRSP Duration (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>5</td>
<td>2.1 (0.1–5.0)</td>
<td>30</td>
<td>12.8 (8.6–18.2)</td>
<td>8</td>
<td>3.4 (1.5–6.7)</td>
</tr>
<tr>
<td>3–12 months</td>
<td>5</td>
<td>1.5 (0.5–3.5)</td>
<td>31</td>
<td>9.2 (6.2–13.0)</td>
<td>7</td>
<td>2.1 (0.8–4.3)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>4</td>
<td>1.8 (0.5–4.5)</td>
<td>13</td>
<td>5.7 (3.0–9.7)</td>
<td>2</td>
<td>0.9 (0.1–3.2)</td>
</tr>
<tr>
<td>NGMN Duration (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>1</td>
<td>0.8 (0.02–4.3)</td>
<td>20</td>
<td>15.5 (9.4–23.9)</td>
<td>5</td>
<td>3.9 (1.3–9.0)</td>
</tr>
<tr>
<td>3–12 months</td>
<td>2</td>
<td>1.6 (0.2–5.7)</td>
<td>7</td>
<td>5.5 (2.2–11.3)</td>
<td>8</td>
<td>6.2 (2.7–12.4)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>1</td>
<td>2.2 (0.1–12.4)</td>
<td>6</td>
<td>13.4 (4.9–29.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ETON Duration (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>0</td>
<td>0</td>
<td></td>
<td>4</td>
<td>10.2 (2.8–26.1)</td>
<td>2</td>
</tr>
<tr>
<td>3–12 months</td>
<td>1</td>
<td>2.6 (0.1–14.7)</td>
<td>3</td>
<td>7.9 (1.6–23.1)</td>
<td>1</td>
<td>2.6 (0.1–14.7)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>1</td>
<td>9.4 (0.2–52.5)</td>
<td>2</td>
<td>18.8 (2.3–68.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>COMP* Duration (months)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>20</td>
<td>2.4 (1.5–3.8)</td>
<td>77</td>
<td>9.3 (7.4–11.7)</td>
<td>30</td>
<td>3.6 (2.5–5.2)</td>
</tr>
<tr>
<td>3–12 months</td>
<td>15</td>
<td>1.4 (0.8–2.3)</td>
<td>81</td>
<td>7.6 (6.1–9.5)</td>
<td>29</td>
<td>2.7 (1.8–3.9)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>10</td>
<td>1.7 (0.8–3.1)</td>
<td>47</td>
<td>7.8 (5.8–10.4)</td>
<td>19</td>
<td>3.2 (1.9–4.9)</td>
</tr>
</tbody>
</table>

Study CHCs: DRSP, NGMN and ETON.
Comparators: LNG10-20, LNG15-30, NETA and NGM.
* COMP includes all four comparators.

34 years of age (HR 2.16, 1.32, 3.54) and of ATE in those 35–55 years of age (HR 2.42, 1.01, 5.82) were consistent with the overall findings with combined comparators.

We also tested individually in the models each of the covariates that had a prevalence of 1% or more in any of the exposure groups (Table 2). None changed the relative hazard estimate by 10% or more so all were excluded from the final models. A test for age interaction was not significant for VTE for new users.

Table 5 shows the incidence rates of study endpoints by duration of use. For VTE, the incidence was highest during the first 3 months of use for DRSP and NGNM, as expected. The number of VTEs was low in all duration time intervals for ETON. For ATE and total mortality, the number of events in each of the duration time intervals was small (≤8) for all of the newer CHCs.

Table 6 shows the association of duration of use on the hazard ratio for the newer CHCs relative to comparators based on Cox proportional hazards regression. As expected, DRSP use of less than 12 months was associated with increased risk of VTE (HR 1.96, 95% CI 1.25–3.70 for <3 months and HR 1.88, 95% CI 1.20–2.93 for 3–12 months). The other increased risks (NGMN >12 months and VTE, ETON >12 months and ATE) occurred in association with small cell sizes and were possibly chance findings.

4. Discussion

The major finding from this population-based cohort of 573,680 women who initiated new use of study CHCs was an increased risk of ATE and VTE associated with DRSP use relative to the use of the four comparator low-dose estrogen CHCs. The increased risk of ATE was present only in the older segment of the cohort (ages 35–55 years), while the increased risk of VTE was restricted to the younger women (ages 10–34 years). We did not find statistically significant associations for NGMN or ETON with any of the endpoints.

Of the four prior studies examining the association of the NGMN transdermal patch with VTE, one showed no increased risk relative to NGM-containing CHC pills [13–15], two showed an approximate doubling of risk relative to either NGM-containing or LNG-containing CHCs [17–19], and one showed no increased risk relative to LNG-containing CHCs in women 39 years or younger, but could not rule out
an increased risk in women ages 40–44 years [16]. Two studies examined NGMN patch use with ATE, but both had small numbers of the endpoints [17,20] and found no association. There have been no published studies of ETON vaginal ring use and ATE.

Another study reporting ATE and death associated with the use of DRSP was the European Active Surveillance Study on oral contraceptives. There were 25 ATEs (none in DRSP users) and 32 deaths associated with a mortality rate of 1.4 per 10,000 [4]. In the present study, we found 14 women who initiated drospirenone-containing oral contraceptives and had an ATE.

It is unclear why the results have been inconsistent regarding the risk of VTE with DRSP. It is likely that some of the variation in study findings relate to methodological differences including whether or not the analyses were restricted to new users, inclusion or exclusion of women with cancer and other serious events which increased risk of thromboembolic events, capability for case adjudication and study size.

The major strengths of this study are inclusion of a large geographically and demographically diverse cohort of new CHC users and the capability to evaluate all three of the newer contraceptive preparations in the same analytic data set. Additionally, the ability to evaluate risk of non-VTE endpoints, namely, ATE and mortality, and the ability to adjudicate endpoints by medical record review were strengths of the study.

Limitations of the study include (a) the assessment of CHC exposure periods based on the electronic pharmacy records of filled prescriptions rather than information on actual intake and (b) the absence of some important covariates. Although electronic pharmacy data may not represent the actual use of the medications, these data have been shown to provide reasonably unbiased information on medication use. We also did have not have access to data on key confounders including obesity, personal and family history of thrombosis, lifetime use of hormonal contraceptives and smoking. However, the studies which have included these variables in their analyses or a subset of them found that estimates of relative risk were not substantively affected [4,5,9].

In summary, we found that the initiation of new use of DRSP-containing CHCs was associated with a 77% increase in the risk of hospitalization for VTE relative to the use of a comparator group of four low-dose estrogen CHCs. Though the absolute incidence of VTE is low, the growing number of studies showing an increased risk of VTE with DRSP suggests that DRSP-containing CHCs should be used cautiously for women seeking hormonal contraception.

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References


