TITLE: Risk of Venous Thromboembolism with Drospirenone/Ethinyl Estradiol Combined Oral Contraceptive Pill versus Other Combined Hormone Contraceptives: Clinical Evidence and Safety

DATE: 11 July 2011

RESEARCH QUESTIONS

1. What is the clinical evidence regarding the risk of venous thromboembolism with a drospirenone/ethinyl estradiol combined oral contraceptive pill versus other combined hormone contraceptives?

2. What is the safety of a drospirenone/ethinyl estradiol combined oral contraceptive pill versus other combined hormone contraceptives?

KEY MESSAGE

There is no clear consensus in the literature as to the safety or relative risk of venous thromboembolism for a drospirenone/ethinyl estradiol combined oral contraceptive pill versus other forms of combined hormonal contraceptives.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 6), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type for research question number 1. Methodological filters were applied to research question number 2 to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2006 and Jun 27, 2011. Internet links were provided, where available.
The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies.

One systematic review, two randomized controlled trials, and seven non-randomized studies were identified regarding the clinical evidence for the safety or risk of venous thromboembolism for the drospirenone/ethinyl estradiol combined contraceptive pill in relation to other combined hormone contraceptives. No relevant health technology assessments were identified. Additional articles that may be of interest can be found in the appendix.

OVERALL SUMMARY OF FINDINGS

Overall, evidence from the randomized controlled trials and non-randomized studies identified is divided on the safety and risks of venous thromboembolism (VTE) in women taking a drospirenone/ethinyl estradiol (DRSP/EE) combined oral contraceptive (COC) in comparison to other combined hormone contraceptives. The authors of the identified systematic review could draw no formal conclusions due to methodological errors inherent in the studies it examined.

Additional study details and the authors’ conclusions can be found in Table 1. No health technology assessments regarding the risk of VTE in women using a DS P/EE COC versus women using combined hormonal contraceptives were identified.

<table>
<thead>
<tr>
<th>Author and date</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Results and Conclusions</th>
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<tbody>
<tr>
<td>Systematic Review</td>
<td>COCs containing DRSP/EE</td>
<td>Other available COCs containing ethinyl estradiol and progestogens</td>
<td>No conclusions could be drawn regarding the relative safety of COCs due to poor study methodology.</td>
</tr>
<tr>
<td>Mohamed, 2011</td>
<td>DRSP 3 mg / EE 0.03 mg</td>
<td>NuvaRing</td>
<td>Differences in blood component profiles were not statistically significant. No clinically relevant adverse effects were observed in either treatment group.</td>
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<tr>
<td>Kluft, 2006</td>
<td>DRSP 3 mg / EE 0.03 mg</td>
<td>Desogestrel 0.150 mg / EE 0.03 mg</td>
<td>Changes in hemostatic variables were similar within all test groups. Changes were less pronounced in the DRSP 3 mg / EE 0.02 mg group. All treatments were considered by the authors to be safe and well tolerated.</td>
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<tr>
<td>Non-Randomized Studies – <em>Evidence of Increased Risk</em></td>
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<tr>
<td><em><em>Jick</em>, 2011</em>*</td>
<td>COCs containing DSRP</td>
<td>COCs containing levonorgestrel</td>
<td>The risk of non-fatal VTE was two times higher in women taking COCs containing DSRP than in women taking COCs containing levonorgestrel.</td>
</tr>
<tr>
<td><em><em>Parkin</em>, 2011</em>*</td>
<td>COCs containing DSRP</td>
<td>COCs containing levonorgestrel</td>
<td>Women using COCs containing DSRP had a threefold higher risk of non-fatal idiopathic VTE than women using COCs containing levonorgestrel. Sub-analysis suggested that confounders were an unlikely explanation.</td>
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<tr>
<td><strong>Lidegaard, 2009</strong></td>
<td>COCs containing DSRP</td>
<td>Many available COCs</td>
<td>For the same estrogen dose and length of use, women using COCs containing DSRP had a significantly higher risk for venous thrombosis than women using COCs containing either levonorgestrel, norethisterone, or norgestimate, but a lower risk than women taking COCs containing either gestodene, desogestrel, or cyproterone.</td>
</tr>
<tr>
<td><strong>Van Hylckama Vlieg, 2009</strong></td>
<td>COCs containing DSRP</td>
<td>Many available COCs</td>
<td>The risk for venous thrombosis for women using COCs containing DSRP was significantly higher than for women using COCs containing either levonorgestrel or gestodene, but less than for women using COCs containing desogestrel.</td>
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<tr>
<th>Non-Randomized Studies – <em>No Evidence of Increased Risk</em></th>
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<tbody>
<tr>
<td><strong>Dinger, 2010</strong></td>
<td>COCs containing DSRP</td>
<td>Dienogest / EE</td>
<td>After adjusting for confounders, the authors determined the risk for VTE was similar amongst women regardless of the COC they used.</td>
</tr>
<tr>
<td><strong>Seeger, 2007</strong></td>
<td>DSRP 3 mg / EE 0.03 mg</td>
<td>Other available COCs</td>
<td>The authors concluded that women using a COC containing DSRP / EE were at a similar risk of developing a VTE as other COC users.</td>
</tr>
<tr>
<td><strong>Dinger 2007</strong></td>
<td>COCs containing DSRP</td>
<td>Other available COCs</td>
<td>Serious adverse and fatal events were rare in women taking COCs containing DSRP and were similar to those associated with other COCs.</td>
</tr>
</tbody>
</table>

* Studies mentioned in the FDA Drug Safety Alert

COC = Combined Oral Contraceptive; DSRP = Drospirenone; EE = Ethinyl Estradiol; VTE = Venous Thromboembolism
REFERENCES SUMMARIZED

Health technology assessments
No literature identified.

Systematic reviews and meta-analyses


Randomized controlled trials


Non-randomized studies


PubMed: PM19679614

PubMed: PM17766604

PubMed: PM17434015

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APPENDIX – FURTHER INFORMATION:

Randomized controlled trials

Cardiovascular risk not specified


Specified comparator absent


Non-randomized studies – specified comparator absent


Guidelines and recommendations


Review articles


Additional articles
