Drospirenone and risk of venous thromboembolism

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Disclosures

- No conflicts of interest
- Temporary voting member for FDA Advisory Committee on drsp and risk of VTE
Objectives

- To discuss the evidence for drospirenone-containing oral contraceptives and risk of venous thromboembolism
- To discuss limitations in the evidence
- To discuss implications for guidance for use of drospirenone-containing oral contraceptives
CHC generations

- **1st generation:**
  - norethynodrel

- **2nd generation:**
  - levonorgestrel, norethindrone, norgestimate, norelgestromin

- **3rd generation:**
  - desogestrel, etonogestrel, gestodene (less androgenic effects, better cardiovascular profile)

- **4th generation:**
  - drospirenone (anti-androgenic and anti-mineralocorticoid activity)
Progestin generations in CHCs

- **1st generation:**
  - norethynodrel

- **2nd generation:**
  - levonorgestrel, norethindrone, norgestimate, norelgestromin

- **3rd generation:**
  - desogestrel, etonogestrel, gestodene (less androgenic effects, better cardiovascular profile)

- **4th generation:**
  - drospirenone (anti-androgenic and anti-mineralocorticoid activity)
Drospirenone-containing COCs

<table>
<thead>
<tr>
<th>Drospirenone</th>
<th>Ethinyl Estradiol</th>
<th>Levomefolate</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg</td>
<td>0.03 mg</td>
<td>0</td>
<td>21/7</td>
</tr>
<tr>
<td>3 mg</td>
<td>0.02 mg</td>
<td>0</td>
<td>24/4</td>
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<tr>
<td>3 mg</td>
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</table>
Drospirenone-containing COCs
RR, OR, or HR and 95% CI

- Dinger, 2007
- Seeger, 2007
- Lidegaard, 2009
- Vlieg, 2009
- Dinger, 2010
- Jick, 2011
- Lidegaard, 2011
- Parkin, 2011
- FDA, 2011
Drospirenone-containing COCs
RR, OR, or HR and 95% CI
VTE incidence in studies of DRSP

Per 10,000 women-years

- 30 mcg ethinyl estradiol
- 20 mcg ethinyl estradiol
Mechanism of CHC increased risk for VTE

- **CHCs increase pro-coagulant factors:**
  - Factor II, VII, VIII, X and fibrinogen

- **CHCs decrease anticoagulants:**
  - Protein S, antithrombin and tissue factor inhibitor
  - Induce resistance to activated Protein C

- **Different CHC formulations have varying effects on these factors**

- **Changes observed with all routes of delivery**
Mechanism of CHC increased risk for VTE

- **Drospirenone**
  - More resistant to anticoagulant effect of activated protein C
  - Increase thrombin generation
  - Blocks aldosterone receptors; aldosterone may decrease coagulability

Van Vliet, J Thromb Haemost, 2004
Limitations

- Contraceptive use patterns
- Attrition of susceptibles
- Channeling bias
- Confounding factors
- Validity of diagnoses
- Referral/diagnostic bias
Absolute rates of VTE

Reid, J Fam Plann Reprod Health Care, 2010
Heinemann, Contraception, 2007
Heit, Ann Int Med, 2005
Jackson, Obstet Gynecol, 2011
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
[Docket No. FDA–2011–N–0002]

Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.
Advisory Committee vote

- **VOTE:** Do you believe that, in the general population of women who desire contraception, the benefits of the DRSP-containing oral contraceptives for prevention of pregnancy outweigh their risks?
  - If not, are there subpopulations of women for whom the risk/benefit profile would be favorable?

  - Yes: 15
  - No: 11
  - Abstain: 0
VOTE: Do you believe the current DRSP labels adequately reflect the risk/benefit profile for these products?

- If not, in general terms, how would you recommend revising the label, for example, provide descriptive data about risk, interpret the findings of the epidemiologic data, provide additional Contraindications or Warnings?

Yes: 5  No: 21  Abstain: 0
“Based on this review, FDA has concluded that drospirenone-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills.”

“Women should talk to their healthcare professional about their risk for blood clots before deciding which birth control method to use. Healthcare professionals should consider the risks and benefits of drospirenone-containing birth control pills and a woman’s risk for developing a blood clot before prescribing these drugs.”

“It is unclear whether the increased risk seen for blood clots in some of the epidemiologic studies is actually due to drospirenone-containing birth control pills.”

FDA. http://www.fda.gov/Drugs/DrugSafety/ucm299305
Updated product label

Ingenix (Hazard Ratio\textsuperscript{a,b,c,d})
EURAS (Hazard Ratio\textsuperscript{e,f,g,h})
LASS (Hazard Ratio\textsuperscript{e,f,g,h})
FDA-funded study (Hazard Ratio\textsuperscript{e,l,r})
Danish (Rate Ratio\textsuperscript{e,l,k,l})
Danish re-analysis (Rate Ratio\textsuperscript{e,l,k})
MEGA study (Odds Ratio\textsuperscript{e,l})
German case-control (Odds Ratio\textsuperscript{f,g,h,k,m,n,o,p})
PharMetrics (Odds Ratio\textsuperscript{g})
GPRD study (Odds Ratio\textsuperscript{f})

Prospective Cohort Studies

Retrospective Cohort Studies

Case-Control Studies

Non-fatal idiopathic cases only
Updated product label

- **Non-Pregnant Non-COC user**: Ranges from 1 to 5
- **COC-User**: Ranges from 3 to 9
- **Pregnancy ***: Ranges from 5 to 20
- **Postpartum (12 weeks only)**: Ranges from 40 to 65

Number of Women with a Blood Clot out of 10,000 Women Years (WY)
Patient labeling

- “Women who use birth control pills with drospirenone (like Yasmin) may have a higher risk of getting a blood clot. Some studies reported that the risk of blood clots was higher for women who use birth control pills that contain drospirenone than for women who use birth control pills that do not contain drospirenone.”
Conclusions

- Increased risk for VTE with drospirenone-containing COCs?

- Consider absolute risk of VTE, VTE risk for pregnancy/postpartum

- Further research
Thank you
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For more information please contact Centers for Disease Control and Prevention

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Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.