Combined Oral Contraceptives (COC) and Venous Thromboembolism (VTE)

ARHP 2010

Carolyn Westhoff, MD
Columbia University
Disclosures

• Dr. Westhoff consults for:
  – Bayer*, Merck*, and Duramed
  – * sponsors of relevant phase IV studies
  – All produce contraceptives to be discussed in this talk

Learning Objectives

• Understand the risk factors for VTE

• Characterize the association between CHC and VTE risk factors

• Describe what we learned about CHC use and VTE risk until 2000.

• Discuss what we have learned about CHC use and VTE risk in the last decade
PubMed Search of OC and Thromboembolism

Pathophysiology of VTE: (DVT and PE)

Deep Vein Thrombosis (DVT)
- Thrombi in deep veins of extremities or pelvis
- Often presents as pain, swelling, in one leg
- May lead to pulmonary embolism (PE), which has much greater mortality

VTE background

• Incidence ~ 14 per 10,000 person-years

• Incidence increases with age

• After one VTE, increased risk of recurrence, and long-term venous impairment

• Main contributing factors are -Stasis of blood flow, -Endothelial damage, and -Hypercoagulability

• Doppler is a painless diagnostic test now in wide use, contributing to higher incidence in recent studies.

Risk Factors for VTE

• Increasing age
• Increasing weight (obesity)
• Family or personal history of VTE
• Genetic mutations affecting coagulation
• Immobilization or surgery
• Long-haul travel
• Estrogen containing contraceptives & HRT
European Active Surveillance Study (EURAS): Increasing Impact of Age and BMI on the VTE Risk in COC Users

- Risk estimates based on 115 VTEs in 116,708 women-years of exposure

Activation

- Fibrinogen,
- Factors V, VII, VIII, X, vWF

Inhibition

- Antithrombin III
- Protein C
- Protein S
- Activated Protein C

EE increases

Adapted from Comprehensive Gynecology, 5th ed. Katz (editor)
OC and VTE – 1960’s-70’s

• 1960 – FDA approval of Enovid
• 1961 – Pulmonary embolism report, Lancet
• 1966 – FDA task force on side effects
• 1969 - The Doctor’s Case against the Pill
• 1970 – Senate hearings about pill safety
• 1970 – FDA mandates package inserts – the first ever for a pharmaceutical product
"The Nelson Pill Hearings"
In 1970, Gaylord Anton Nelson, a Democratic Senator from Wisconsin, called for Congressional hearings on the safety of combined oral contraceptive pills.
OC’s and VTE – 1980’s

• Larger studies with improved methods starting to report results. RR range 3-11.

• Study critiques emerging

• Pertinent factors: Current use rather than past use. Effect of estrogen dose still unclear. Duration of use does not matter (sic).

Realini & Goldzieher, AJOG, 1985; Vessey BMJ, 1986
OC’s and VTE – 1990’s

• Gerstmann and colleagues
  – 230,000 women 15-44 from 1980-86

<table>
<thead>
<tr>
<th>EE dose</th>
<th>Rate of VTE/10,000 WY</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50μg</td>
<td>4.2</td>
</tr>
<tr>
<td>50μg</td>
<td>7.0</td>
</tr>
<tr>
<td>&gt;50 μg</td>
<td>10.0</td>
</tr>
</tbody>
</table>

– Data consistent with earlier studies associating the dose of EE to the risk of VTE; background rate of 0.8/10,000 WY

*Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. AJE 1991.*
OC and VTE- 1990’s

• WHO publication in the Lancet in 1995 was a case-control study suggesting that women using OC formulations with the progestins desogestrel and gestodene had a 1.5-2.5 higher risk of VTE compared to users of levonorgestrel preparations with <50μg EE

1990’s Pill Scare

Documented increase in abortion rates in UK, Norway, other countries
No decrease in VTE among young women.
1990’s in summary

• Importance of EE dose established
• First studies to compare individual pill brands
• RR with OC use about 2-3
• RR with pregnancy about 6
• Vigorous critiques of study methodology
• New covariates (eg, Factor V)
• NEW understanding of role of duration of use
2000’s

• Do non-oral routes of CHC delivery and new formulations decrease risk of VTE?
• Fatal PE reported in teenaged patch user
• PK shows patch has more EE than pill and ring
• RR of VTE with patch compared to OCs, range 1.1 – 2.2.
• FDA label change – “this product exposes women to higher levels of estrogen than most birth control pills.”

May 7, 2004: 14-year-old Becomes Youngest Ortho Evra® Victim

Eighth-grader Alycia Brown dies of a blood clot in her lower pelvis after using the Ortho Evra® patch for about eight weeks. Only 14 years old, Brown becomes the product’s youngest known fatality.
FDA mandated post-approval surveillance studies - 1.

Prospective cohorts with active surveillance:
Large enough to assess differences in risk between preparations.

Lifetime history of COC use

Complete documentation of relevant risk factors

Documentation & blinded adjudication of all VTEs

Validation of all patient-reported outcomes with attending physician
FDA mandated post-approval surveillance studies – 2.

• Prospective or Retrospective cohort studies:
• Use electronic databases
• Potential to be nimble
• In some, can compensate for lack of confounder information w nested case-control and propensity scores.
Newest studies

• EURAS, Dinger, 2007
• Ingenix, Seeger 2007
• MEGA(case-control), v. Hylckama Vlieg, 2009
• Danish National study, Lidegard, 2009

• Consensus statement, Reid, 2010

• INAS, underway
• Nuvaring cohort, underway
## EURAS Study Design

<table>
<thead>
<tr>
<th>Design</th>
<th>Location</th>
<th>N</th>
<th>Cohorts</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective non-interventional active</td>
<td>7 European countries 2000-2005</td>
<td>60,000 women</td>
<td>Yasmin, LNG- COCs, Other COCs, Only initiators or switchers to new</td>
<td>Independent investigator and advisory board</td>
</tr>
<tr>
<td>surveillance controlled cohort study</td>
<td></td>
<td>140,000 woman-years (WY)</td>
<td>product included</td>
<td></td>
</tr>
</tbody>
</table>

EURAS: Distribution of VTEs

Reported: 522 (100%)
Confirmed: 118 (23%)
Not Confirmed: 404 (77%)

VST – venous sinus thrombosis
PE – pulmonary embolism
DVT – deep venous thrombosis

EURAS: Preferential Prescribing of Yasmin to Women with Risk Factors for VTE

EURAS: VTE Incidence and Hazard Ratio

EURAS: Duration of Use Impact on VTE Risk

VTE Incidence vs. Duration of Use

Adapted from Dinger et al. Contraception 75 (2007) 344–354
**Ingenix: Study Design**

<table>
<thead>
<tr>
<th>Design</th>
<th>Location</th>
<th>N</th>
<th>Cohorts</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective observational cohort study</td>
<td>US</td>
<td>67,000 women, 42,000 woman-years (WY)</td>
<td>Yasmin initiators Other COC initiators</td>
<td>Incidence rates and rate ratios for thromboembolic events</td>
</tr>
</tbody>
</table>

Ingenix: Methodological Considerations

Electronically captured provider, facility, and pharmacy claims from US insurance plans

Matching of Yasmin to two-fold larger group of other COC users (using propensity scores)

Claims-based outcomes confirmed via abstraction of relevant medical records

Ingenix: Incidence of VTE was Similar Between Yasmin and Other COC Cohorts

Ingenix: Yasmin Users Do Not Have a Higher Risk of VTE Compared to Other COC Users

Incidence Rate Ratio – Yasmin vs Other COC (95% CI)

VTE Risk for Yasmin: EURAS & Ingenix

Yasmin vs Other COCs

Exposure = >180,000 WY in 125,000 women

VTE Rate Ratios ITT Analysis (95% CI)

Danish National Registry:
Study Design

<table>
<thead>
<tr>
<th>Design</th>
<th>Location</th>
<th>N</th>
<th>Cohorts</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective national database cohort study</td>
<td>Denmark 1995-2005</td>
<td>10.4 million woman-years in total 3.3 million woman-years in receipt of COC</td>
<td>All fertile Danish women</td>
<td>Rate ratios for all 1st time DVT and PE, portal thrombosis, thrombosis of caval and renal vein</td>
</tr>
</tbody>
</table>
Danish National Registry: Risk for VTE for Various Progestogens

For COCs containing 30-40 μg EE and adjusted for length of use

<table>
<thead>
<tr>
<th>Progestin</th>
<th>adj RR (95% CI)</th>
<th>Crude incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levonorgestrel</td>
<td>Reference</td>
<td>5.8/10,000 WY</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>1.64 (1.27-2.10)</td>
<td>7.8/10,000 WY</td>
</tr>
<tr>
<td>Gestodene</td>
<td>1.86 (1.59-2.18)</td>
<td>7.0/10,000 WY</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>1.82 (0.96-1.47)</td>
<td>6.5/ 10,000 WY</td>
</tr>
</tbody>
</table>

Lidegaard, O et al. BMJ 2009;339:b2890
Danish National Registry Study: Duration of Use Impact on VTE Risk

- Lack of first year effect for LNG only

Observation years, number of venous thromboembolism events, crude incidence rate per 10,000 user years, and adjusted* rate ratios (95% confidence intervals) of venous thromboembolism in current users of combined oral contraceptives according to estrogen dose, progestogen type, and length of use, with non-users of oral contraceptives as reference group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Norethisterone</th>
<th>Levonorgestrel</th>
<th>Norgestimate</th>
<th>Desogestrel</th>
<th>Gestodene</th>
<th>Drospirenone</th>
<th>Cyproterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen 30 - 40 µg</td>
<td>2.81 (1.66 to 4.77)</td>
<td>1.91 (1.31 to 2.79)</td>
<td>3.37 (2.38 to 4.76)</td>
<td>5.58 (4.13 to 7.55)</td>
<td>4.38 (3.65 to 5.24)</td>
<td>7.90 (5.65 to 11.0)</td>
<td>6.68 (4.50 to 9.94)</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>1.76 (1.12 to 2.77)</td>
<td>2.23 (1.78 to 2.78)</td>
<td>2.27 (1.74 to 2.96)</td>
<td>3.48 (12.74 to 4.42)</td>
<td>3.85 (3.39 to 4.36)</td>
<td>2.68 (1.86 to 3.86)</td>
<td>3.24 (2.28 to 4.61)</td>
</tr>
<tr>
<td>1-4 years</td>
<td>1.55 (0.83 to 2.08)</td>
<td>1.91 (1.55 to 2.36)</td>
<td>2.20 (1.70 to 2.85)</td>
<td>3.19 (2.53 to 4.02)</td>
<td>3.34 (2.95 to 3.78)</td>
<td>3.26 (2.35 to 4.54)</td>
<td>3.37 (2.38 to 4.76)</td>
</tr>
</tbody>
</table>

*All estimates adjusted for age, calendar year, and education and with non-users of oral contraceptives as reference group.

Adapted from Lidegaard O et al, BMJ 2009;339:b2890: Table 2
Danish study limitations

- No information of OC use prior to 1995, thus cannot account for exact duration of use.
- No information available regarding confounders (eg, obesity)
- VTEs in registry database cannot be confirmed in 31%-71% of cases.

Reid, 2010; Severensin, 2010
## MEGA Study Design

<table>
<thead>
<tr>
<th>Design</th>
<th>Location</th>
<th>N</th>
<th>Cohorts</th>
<th>Clinical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population based, case-control</td>
<td>6 anticoagulation clinics in Netherlands March 1999-Sept 2004</td>
<td>1524 patients 1760 controls</td>
<td>Premenopausal women &lt;50 Not pregnant or 4 weeks postpartum Not using IUD or depot contraceptive</td>
<td>First objectively diagnosed episodes of DVT or PE</td>
</tr>
</tbody>
</table>

MEGA Study:
Risk for VTE for Various Progestogens

Adapted from Van Hylckama Vlieg, A. BMJ 2009;339:b2921: Table 3 – Risk of VTE associated with different types of progestogens in combined oral contraceptives
MEGA study limitations

• C/C study designed to evaluate environmental and genetic factors.
• This is a post-hoc substudy.
• Controls were partners of male cases.
• Duration of use information incomplete.
• In product comparisons, cases are few and thus confidence intervals are wide.
FDA conclusions on 4 studies: additions to the Yasmin label

• 2 prospective cohort studies showed a comparable risk of VTE in Yasmin users to other OC users....

• 2 other studies suggested that the risk of VTE in Yasmin users was higher... HOWEVER... small numbers make the risk estimates unreliable, ... and estimates of duration of use may NOT BE RELIABLE

www.accessdata.fda.gov/drugsatfda_docs/label/2010/021098s017lbl.pdf
## Putting the VTE Risk into Context

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Non-pregnant non-users</th>
<th>COC users</th>
<th>Pregnant non-users</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE incidence</td>
<td>4.7/10,000 women</td>
<td>9.1/10,000 women</td>
<td>29.1/10,000 women</td>
</tr>
</tbody>
</table>

What’s next?

• Cohort studies in progress:
  – US/Euro cohort of Yaz and Yasmin users (INAS)
  – Cohort of Nuvaring users
  – No phase IV cohort of patch users.
• FDA requires “PASS” for all new products.
• Will new estrogens lead to different risk?
• extras
WERE YOU MISINFORMED?
RISKS YOU WERE UNAWARE OF

YAZ SIDE EFFECTS CAN INCLUDE:
- Heart Attack, Seizures & Stroke
- Kidney Failure or Pulmonary Embolism
- Deep Vein Thrombosis (DVT)

CALL (866) 761-1385
TO SPEAK WITH A LAWYER ABOUT YOUR CASE

Did You or Someone You Love Suffer From Gallbladder Problems, A Stroke, or a Heart Attack While Taking Yaz, Yasmin, or Ocella?

If so, you may be entitled to monetary compensation.

Click here to find the right birth control pill lawyer, or call 888-315-3997 now.

Have you or a loved one been effected by Yaz or Yasmin?
Let Napoli Bern Ripka fight for your rights:
- Yaz and Yasmin Birth Control Pills
- Suffering from Side Effects Due to Yaz or Yasmin?
- You may be entitled to compensation from the manufacturer

Fill out the form for a FREE CONSULTATION with one of our lawyers who can see if you are entitled to be compensated.
‘Left-censoring’ changes in observation of VTE risk

- Start of observation for ‘new’, recently launched preparations (e.g., DRSP)
- Start of observation for ‘old’, well established preparations (e.g., LNG)
Potential Misclassification of Duration of Use in LNG Users in the Danish Study