Combined hormonal contraception and VTE

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Learning objectives:

Pathophysiology, pharmacology, and epidemiological data

Is there a difference between various brands?

Definitions

• **Venous Thromboembolism (VTE):**
  - A condition in which a blood clot (thrombus) forms in a vein, most commonly in the deep veins of the legs or pelvis:
    - Deep Vein Thrombosis (DVT)
  - The thrombus can dislodge to the pulmonary arteries:
    - Pulmonary Embolism (PE)

VTE Clinical synthesis

1. Determine level of probability: Wells score
2. Confirm the clot: D-dimer test
3. Find the clot: imaging
   - DVT: calf or thigh
   - DVT: radio-opaque venogram calf
   - DVT: MRI direct thrombosis imaging calf
   - PE: ventilation/perfusion scan
   - PE: helical CT pulmonary angiography
   - PE: MRI direct thrombosis imaging

VTE

- **DVT**
  - Typically in the lower leg
  - Often asymptomatic or associated with minimal symptoms
  - Often undiagnosed
- **PE**
  - Potentially life threatening
- **VTE** is fatal in 1–2% of cases

NI CE 2012

Deep Vein Thrombosis

Adapted from: www.icsi.org 2012
www.nice.org.uk 2012
VTE Multiple hit hypothesis

More than one risk factor is present at any one time

VT: Genetic risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Prevalence</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiden fact V hetero</td>
<td>6%</td>
<td>8</td>
</tr>
<tr>
<td>Leiden fact V homoz</td>
<td>0.2%</td>
<td>64</td>
</tr>
<tr>
<td>Protein C insufficiency</td>
<td>0.2%</td>
<td>15</td>
</tr>
<tr>
<td>Protein S insufficiency</td>
<td>&lt;0.1%</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Antithrombin III insuff.</td>
<td>0.02%</td>
<td>50</td>
</tr>
<tr>
<td>Prothrombin 20210A</td>
<td>2%</td>
<td>3</td>
</tr>
<tr>
<td>Hyperhomocysteinaemia</td>
<td>3%</td>
<td>3</td>
</tr>
</tbody>
</table>

VT: Acquired risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Prevalence</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥30 vs &lt;30</td>
<td>50%</td>
<td>2.5</td>
</tr>
<tr>
<td>Adiposity (BMI&gt;25)</td>
<td>30%</td>
<td>2</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>30%</td>
<td>3-6</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>8%</td>
<td>2</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>4%</td>
<td>8</td>
</tr>
<tr>
<td>Medical diseases</td>
<td>5%?</td>
<td>2-5</td>
</tr>
<tr>
<td>Immobilisation/trauma</td>
<td>?</td>
<td>2-10</td>
</tr>
</tbody>
</table>

Venous Thrombosis: Absolute risk figures

- No OC no pregnancy:
  - 1 event per 10,000 women per year

- OC use:
  - <4 events per 10,000 users per year

- Pregnancy:
  - 6-7 events per 10,000 women per year

OC and VTE

It has been recognized for over 40 years now that the use of combined oral contraceptives (OC) is associated to excess risk of thromboembolic disease, and specifically of venous thromboembolism (VTE). In the 1960’s. Such an excess risk was attributed to the estrogen dose of various OCs, and this led to the reduction of estrogen doses in the late 1960’s and early 1970’s.
The Challenges

- Mid-90’s focused attention on progestins; DSG & GSD (3rd generation) increased in some studies risk over LNG (2nd generation)

- Since then for each new progestogen (3rd and 4th generations) some studies have found increased risk over 2nd generation/LNG

<table>
<thead>
<tr>
<th>Progestogens</th>
<th>Except</th>
<th>&lt;50</th>
<th>&gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>-</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Second</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Third</td>
<td>1.8</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.9</td>
<td>1.6</td>
<td>1.9</td>
</tr>
</tbody>
</table>

VTE risk in relation to estrogen dose and type of progestogen vs nonusers

OCs and SHBG changes

OC and VT: Progestin type

Relative risk versus non-use
OC and CVD
The role of bias

- Prescribing practice
- Healthy user effect (recency)
- Genetic Predisposition
- Biological plausability

Danish Cohort Study:
VTE Time Pattern vs. Progestagen Type

VT and drospirenone

<table>
<thead>
<tr>
<th>VT</th>
<th>Risk /10,000</th>
<th>Rate ratio DRSP/2nd</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dinger⁰⁷</td>
<td>118</td>
<td>9.1 (0.6-1.8) 4th/2nd</td>
</tr>
<tr>
<td>Seege⁰⁷</td>
<td>57</td>
<td>13.0* (0.5-1.6) 4th/2nd</td>
</tr>
<tr>
<td>Vlie⁰⁹</td>
<td>1,524</td>
<td>na (0.7-3.9) 4th/2nd</td>
</tr>
<tr>
<td>Lidegaard⁰⁹</td>
<td>4,213</td>
<td>7.8 (1.3-2.1) 4th/2nd</td>
</tr>
</tbody>
</table>

BMJ
RESEARCH

Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9

Abstract

Venous thromboembolism was not increased with use of progesterone-only pills.
Relative risk versus non-use
Confirmed events only

<table>
<thead>
<tr>
<th>Event Type</th>
<th>VT Rate</th>
<th>IR Rate</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinger07</td>
<td>118</td>
<td>9.1</td>
<td>1.0 (0.6-1.8)</td>
</tr>
<tr>
<td>Vlieg08</td>
<td>1,524</td>
<td>na</td>
<td>1.7 (0.7-3.9)</td>
</tr>
<tr>
<td>Parkin09</td>
<td>61</td>
<td>2.3</td>
<td>2.7 (1.5-4.7)</td>
</tr>
<tr>
<td>Jick11</td>
<td>186</td>
<td>3.1</td>
<td>2.8 (2.1-3.8)</td>
</tr>
<tr>
<td>FDA Kaiser11</td>
<td>625</td>
<td>7.6</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>Gronich11</td>
<td>51</td>
<td>8.6</td>
<td>1.7 (1.0-2.7)</td>
</tr>
</tbody>
</table>

IR = incidence per 10,000 women years

EURAS-OC and Ingenix studies

- **EURAS-OC study**:
  - Large, European-based multinational study (60,000 women; 140,000 women-years)
  - Prospective (2000-2005)
  - Non-interventional
  - Active surveillance
  - Controlled cohort study

- **Ingenix study**:
  - Large, US-based study (67,000 women; 42,000 women-years)
  - Prospective (2001-2004)
  - Controlled cohort data base study
  - Propensity score matching

Both studies compared the cardiovascular safety (VTE) of EE/DRSP with other OCs

EURAS-OC and Ingenix studies: main results

VTE rate ratios (intention-to-treat analysis) and 95% CI

EURAS: VTE Time Pattern vs Progestagen Type

OC and CVD

- Biological plausability
Different effects of oral contraceptives containing different progestogens on protein S and tissue factor pathway inhibitor.


Journal of Thrombosis and Haemostasis
Volume 6 Issue 2 Page 346-351, February 2008

Conclusions: This study observed that the differences in APC resistance induced by OC containing different progestogens can at least in part be explained by different effects of OC on free protein S and TFPI.
Recent epidemiological findings?

Hormonal contraception and venous thrombosis

- VTE is rare in women who low-dose hormonal contraception
- Risk is 50% higher the first year (beware of shifts)
- In COC 40 to 20 mcg EE translates to 18% risk reduction
- The risk of VTE in women who take low-dose OCs is lower than that during pregnancy and child birth
- Looking at all data the risk of VTE compares well among the 3rd and 4rd. generations OC and (slightly) increased compared to 2 generation types (RR 2)

Take home message:

- Tell them...
  - Although relative risk may appear alarming the absolute risk is small
  - Individual guidance minimizes thrombotic risk
  - A balanced view on risks and benefits is mandatory
  - The pill offers additional health benefits
  - It has opened the door to modern contraception and empowering of women

Thank you!

Vinogradova vs Lidegaard

VTE confirmed

<table>
<thead>
<tr>
<th></th>
<th>Vinogradova</th>
<th>Lidegaard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non use</td>
<td>1 reference</td>
<td>1 reference</td>
</tr>
<tr>
<td>COC levonorgestrel</td>
<td>3.0 (2.8-3.3)</td>
<td>3.0 (2.2-4.0)</td>
</tr>
<tr>
<td>COC norgestrel</td>
<td>3.5 (2.9-4.4)</td>
<td>3.5 (2.9-4.3)</td>
</tr>
<tr>
<td>COC desogestrel</td>
<td>6.2 (6.0-7.7)</td>
<td>6.0 (6.0-7.8)</td>
</tr>
<tr>
<td>COC gestodene</td>
<td>6.5 (6.0-8.4)</td>
<td>6.2 (6.0-7.6)</td>
</tr>
<tr>
<td>COC drospirenone</td>
<td>6.1 (4.7-7.8)</td>
<td>6.4 (4.7-7.5)</td>
</tr>
<tr>
<td>COC cyproterone</td>
<td>6.0 (4.7-7.7)</td>
<td>6.4 (4.7-7.9)</td>
</tr>
</tbody>
</table>

Vinogradova et al. BMJ 2015; 350: h2136
Lidegaard et al. BMJ 2011; 345: d6423
Conflicting results have also been found for drospirenone. Two large-scale prospective cohort studies (Fig. 11) [9, 123] and a German case-control study [117] showed no higher risk, while two studies published in 2009 – a retrospective cohort study in Denmark [57] and a Dutch case-control study [113] – showed a slightly higher risk compared to levonorgestrel-containing preparations. The two latter studies, however, exhibit substantial methodological shortcomings [124, 125]. The Dutch study was not statistically significant, and also not representative for either the cases or controls. In the Danish study, short-term and long-term use were misclassified to a considerable degree, and information about important risk factors was not available. In addition, an independent validation study showed that probably around 30% of the diagnoses that the authors took from the Danish patient registry were incorrect [126]. In addition, shortly before this statement went to press, the Boston Collaborative Drug Surveillance Program published the results from two retrospective case-control studies in the USA and England using the PharMetrics [127] and GPRD databases [128]. Both studies yielded higher risk estimates for drospirenone-containing COCs with 30 µg EE. These studies too show considerable shortcomings. The GPRD results, which are based on confirmed VTE, are not statistically significant. The incidence rates, which are too low overall, show that the database compiled only some of the VTE (possible 'ascertainment bias'). In addition, the substantially different risk estimates for pulmonary embolism and deep venous thrombosis (factor 4) indicate the presence of considerable differential diagnostic bias. The PharMetrics study was based on non-confirmed VTE from a database used for calculating benefits, which cannot provide a reliable scientific basis unless the diagnoses are confirmed by health records. The study was not able to reproduce known risks such as the dependence on duration of use (see above), and did not have access to information on major prognostic factors.

In sum, the VTE risk of drospirenone-versus levonorgestrel-containing COCs cannot be conclusively ascertained. The studies with the best methodology do not