Combined pills and venous thromboembolism – what are first choice preparations?

Professor Ian Milsom, M.D., Ph.D.
Dept. of Obstetrics & Gynecology
Sahlgrenska Academy
Gothenburg University,
Gothenburg, Sweden

ORAL CONTRACEPTIVE PILL
- Approved by FDA, November 1959
- First commercially sold in the USA, Spring 1960
- Introduced in Europe, 1961

New oral contraceptive combinations
Successive decrease in estrogen dose
Development of new progestogens

COC’s have been reported to convey several potential non-contraceptive health benefits
- Reduces risk of endometrial cancer and ovarian cancer
- Reduces or eliminates ovulation pain & ovarian cysts
- Reduces or eliminates dysmenorrhoea
- Reduces premenstrual symptoms
- Reduces menstrual bleeding, less anemia
- Reduction in acne/hirsutism
- Reduces risk of extrauterine pregnancy
- Reduced risk for endometriosis and salpingitis?
- Better future fertility

BUT……COC’s have also been reported to have some potential negative side effects
An increased occurrence of venous thromboembolism was first reported in the 1960’s
COC and VTE
Odds ratio

<table>
<thead>
<tr>
<th>Study</th>
<th>OR or RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inman 1968</td>
<td>7.7</td>
</tr>
<tr>
<td>Vessey 1968</td>
<td>9.4</td>
</tr>
<tr>
<td>Vessey 1986</td>
<td>&lt; 50 µg</td>
</tr>
<tr>
<td></td>
<td>&gt; 50 µg</td>
</tr>
<tr>
<td>Gertsman 1990</td>
<td>50 µg</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 µg</td>
</tr>
<tr>
<td>Thorogood 1992</td>
<td>&lt; 50 µg</td>
</tr>
</tbody>
</table>

The importance of oestrogen content
Oral contraceptives and thromboembolic disease:
Effects of lowering oestrogen content
Böttiger LE, Boman G, Ekland G, Westerholm B

Studies published 1995-96 indicating a difference in the risk for VTE between different COC’s
WHO Study
Transnational Study
Boston Collaborative Drug Surveillance Program

COC nomenclature
1st generation
COC with ≥ 50 µg ethinyl estradiol

2nd generation
COC with < 50 µg ethinyl estradiol in combination with levonorgestrel or norethisterone

3rd generation
COC with < 50 µg ethinyl estradiol in combination with desogestrel, gestodene or norgestimate

4th generation
COC with < 50 µg ethinyl estradiol in combination with drosperinone

RR or OR for VTE
3rd generation pills compared to 2nd generation pills

Adjusted for exact age and duration of use

WHO 95
Jick 95
Blomenkamp 95
Spartan 96
Farmer 96
Blomenkamp 95

Jick 90
Farmer 97
Lidegaard 98
Farmer 98
Farmer 00
Suissa 97
### Public Health Consequences

#### Estimated that 50% of women with DVT will develop post-thrombotic syndrome at some time in their lives

**Fatality rate 1-2%**

**Excess number of cases related to desogestrel/gestodene containing OC’s 1-4 per million women treated one year**

*EMEA 2001*

---

**Risk of Thromboembolism with Cyproterone or Levonorgestrel Contraceptives**

*Vasilakis-Scaramozza et al. Lancet 2001;358:1427-29*

Four-fold increase with COC containing 2 mg cyproterone acetate in combination with 35µg EE compared to COC containing 150µg levonorgestrel combined with 30µg EE

---

**The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142 475 women-years of observation**

*Dinger JC et al. Contraception 2007;75:344-354*

Cox regression analysis of hazard ratios for DRSP-containing OC’s vs LNG-containing OC’s:

- 1.0 and 0.8 (Upper 95% CI 1.3-1.8) for venous thromboembolism
- 0.3 and 0.3 (Upper 95% CI 1.2-1.5) for arterial thromboembolism

**Conclusion**

Risks similar for DRSP- and LNG-containing OC’s

---

**The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study**

*Van Hylckama Vlieg A et al. BMJ 2009;339:b2921*

OC’s increase risk (OR 5.0 CI 4.2-5.8)

Compared to non-users:

- LNG-containing OC’s (OR 3.6 CI 2.9-4.6)
- GSD-containing OC’s (OR 5.6 CI 3.7-8.4)
- DRSP-containing OC’s (OR 6.3 CI 2.9-13.7)
- CPA-containing OC’s (6.8 CI 4.7 -10.0)
- DSG-containing OC’s (OR 7.3 CI 5.3-10.0)

---

### Public Health Consequences

#### Baseline incidence, women 15-44 years

**5-10/100,000 woman-years**

Women, 15-44 years, using levonorgestrel containing OCs

20/100,000 women-years

Users of desogestrel/gestodene containing OCs

1.5-2.0, additional 10-20 cases?

First-time users of desogestrel/gestodene containing OC’s

RR 3.0, additional 40 cases?

*EMEA 2001*
Hormonal contraception and risk of venous thromboembolism
Lidegaard Ø et al. BMJ 2009;339:b2890

Overall absolute risk of thrombotic events:
3.01/10,000 women years in non-users
6.29/10,000 women years in current OC users

Rate ratio compared to OC users using a LNG-containing OC and same dose of oestrogen:
- Norgestimate (0.98 CI 0.71-1.37)
- DRSP (1.84 CI 1.27-2.61)
- DSG (1.82 CI 1.49-2.22)
- GSD (1.86 CI 1.59 – 2.18)
- CPA (1.88 CI 1.47 -2.42)

VENOUS THROMBOEMBOLISM

- New OC/HRT combinations
- VTE UNCOMMON EVENT
- How can we predict risk of VTE
- Analysis of coagulation factors
- Marker of "total estrogenicity"?
- SHBG-most commonly used marker widely available for all products

The risk of VTE has been demonstrated to be related to the estrogen component of COC in a dose dependent manner

How does one explain a possible association with the gestagen component

HYPOTHESIS-ESTROGENICITY-OC/HRT

- Total estrogenicity of product
- Sum of estrogen component type of estrogen - potency & dose + progestogen component type of progestogen & dose

The risk of venous thromboembolism in current users of COCs with desogestrel or gestodene (upper) and drospirenone (lower) versus COCs with levonorgestrel (95% CI indicated)

New OC/HRT combinations
VTE UNCOMMON EVENT
How can we predict risk of VTE
Analysis of coagulation factors
Marker of "total estrogenicity"?
SHBG-most commonly used marker widely available for all products

The risk of VTE has been demonstrated to be related to the estrogen component of COC in a dose dependent manner

How does one explain a possible association with the gestagen component

Incidence of VTE/100,000 woman years

% increase in SHBG
"A low dose monophasic COC containing levornorgestrel is recommended for first time users."

Swedish MPA 2005

"All combined oral contraceptives are equally effective in preventing pregnancy. Millions of women in Europe use oral contraceptives, so use of the pill with the best safety profile in terms of thrombosis would probably prevent thousands of thrombotic events and hundreds of deaths a year. The safest oral contraceptive is one that contains the lowest tolerable dose of ethinyl estradiol (lowest dose that prevents breakthrough Bleeding - 30 µg) together with the second generation progestogen, levonorgestrel."

F Helmerhost & FR Rosendaal BMJ 2013

Is this the end of the story????

- Decreasing the estrogen content of COC’s has reduced the risk of VTE
- COC’s have until recently all contained ethinyl estradiol (EE)
- Two COC’s containing estradiol are now available
- Is the risk for VTE lower with estradiol containing pills (E2+DNG or E2+NOMAC)
Combined pills and venous thromboembolism – what are first choice preparations?

- Low dose monophasic pill containing 30µg or preferably 20µg EE in combination with levonorgestrel
- Important that other COC’s freely available - individualise treatment
- Estradiol containing COC’s look potentially useful but more data needed
- Not only important to choose the right COC but more important to choose the right patient – importance of history taking
- Women with increased risk of VTE should use progestogen only contraception or Cu-IUD

SAFE PATIENTS!
SAFE PILLS!