19 February 2013

POSITION STATEMENT

Diane-35 and Risk of Venous Thromboembolism (VTE)

Introduction

Cyproterone acetate (2mg) combined with ethinylestradiol (35μg) (CPA/EE), a product commercialized in Canada under the name of Diane-35, was introduced worldwide in 1978. CPA is a progestogen with strong anti-androgenic properties that may also be used as a mono substance in the dosage of 10 mg to 100 mg to treat women with moderate to severe signs of androgenization (hirsutism, acne).1,2 Men are also prescribed high doses of CPA (50-300 mg) for the treatment of prostate cancer.3 In Canada, CPA/EE was approved in September 1997 for the treatment of pronounced forms of acne, accompanied by seborrhoea, inflammation or formation of nodes, mild forms of hirsutism and for whom treatment with oral antibiotics or other available treatments has not worked.4,5 In addition to its effect on androgenic diseases, CPA/EE is known to be an effective combined hormonal contraceptive.6

Recently, there have been concerns about the relationship between CPA/EE and the risk of venous thromboembolic diseases (VTE) and related death. As a result, Health Canada issued an announcement that they would review the safety of the drug Diane-35 as of January 31, 2013.7

The absolute risk of blood clots for individual women is very low (4-5/10,000). The risk of getting a blood clot due to combined hormonal contraceptives is between 8-9 women per 10,000 pill users every year.8 Of 100 women who get a blood clot, it is estimated that one person will die, for a death rate of < 1 per 100,000 combined hormonal contraceptive users per year. Pregnancy carries a host of potential risks including higher rates of blood clots than that experienced by combined hormonal contraceptive users. Women who are overweight or pregnant have a risk of blood clots that is 2 to 40 times higher than the risk of blood clots associated with combined hormonal contraceptive use.9,10,11 To put the risks of combined hormonal contraceptive related deaths (0.5-0.9 per 100,000 users per year) into perspective, consider the following statistics12:

<table>
<thead>
<tr>
<th></th>
<th>Deaths/100,000 women per yr</th>
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<tbody>
<tr>
<td>Smoker (35 yr)</td>
<td>167</td>
</tr>
<tr>
<td>Road deaths</td>
<td>8</td>
</tr>
<tr>
<td>Household accidents</td>
<td>4</td>
</tr>
<tr>
<td>Per 100,000 combined hormonal contraceptive users with Leiden V</td>
<td>1.9 -- 4</td>
</tr>
<tr>
<td>Per 100,000 combined hormonal contraceptive users</td>
<td>0.5 - 0.9</td>
</tr>
<tr>
<td>Background risk of fatal VTE for women aged 15-44</td>
<td>0.6</td>
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The SOGC regularly reviews the scientific literature that addresses the risks of VTE with therapeutic products used in gynaecology and provides this update as of February 2013.
The Evidence

The ideal study to address the risk of VTE with a new product would compare VTE rates in similar women (similar age, weight, etc.) with similar risk factors (smoking, obesity, family history, etc.) initiating combined hormonal contraceptives for the first time (longer term users have lower risks than women starting the pills) with active follow-up (regular phone calls to identify any possible complications) and finally, with validation of any possible complications (by reviewing the actual medical record). Normally, this type of high quality information is only available when the study is planned in advance to address all these concerns in prospective fashion.

We have reviewed the published data on the issue of VTE and CPA/EE in the context of this recent “pill scare” about VTE risks associated with combined hormonal contraceptives. These studies include both prospective and retrospective studies of variable quality. Eight studies published from 1995 to 2004 included women using CPA/EE and other types of combined hormonal contraceptives related to VTE. As reviewed by WO Spitzer, professor of epidemiology at McGill University, the range of absolute incidence rates of VTE among CPA/EE users in these studies varied from 1.2 to 9.9 per 10,000 women-years. The absolute risk difference between CPA/EE users and conventional combined hormonal contraceptive users, called attributable risk, was not higher than 0.04%, indicating that CPA/EE users may have up to 0.04% more risk of getting a VTE than users of conventional combined hormonal contraceptives. In summary, except for one study exhibiting a small statistically significant benefit, there was no difference between the incidence rates of VTE among CPA/EE users and those among conventional combined hormonal contraceptive users.

One study restricted its analysis to women with acne, hirsutism, and polycystic ovary syndrome (PCOS) and estimated the risk of VTE in users of CPA/EE and in users of conventional combined hormonal contraceptives. The authors reported a statistical difference in incidence rate of VTE, with an incidence rate of 8.05 per 10,000 women-years in CPA/EE users while it was 3.7 per 10,000 women-years in women using conventional combined hormonal contraceptives. Interestingly, two recent studies showed that women who suffer from PCOS were more likely to have VTE than women without PCOS.

Conclusion

When examining the relationship between CPA/EE and VTE-associated risk, it is important to examine the strength of the evidence. Fear and confusion resulting from media coverage of rare events (death from combined hormonal contraceptive induced VTE of < 1/100,000) has the potential to create harm as inadvertent pregnancies are often the result of panic stopping of combined hormonal contraceptives and these pregnancies themselves carry greater risks for VTE. This situation occurred in 1995 following the publication of three articles in The Lancet. According to Mills, in the UK alone, there were 30,000 more conceptions in the 9 months following the “pill scare” (deliveries increased by 20-25% and abortions reached the highest level in 30 years with 10,000 more than anticipated). Mills and Edwards argued convincingly that “the constant negative drip of information from the lay press makes it impossible for the professionals and consumers to interpret true risks and benefits of drugs.” Combined hormonal contraceptives are known to reduce the risk of pelvic inflammatory disease, ectopic pregnancy, anemia, endometrial and ovarian cancer, and acne. CPA/EE, in particular, is one of the most effective and safest treatments for acne in women of reproductive age and because of its contraceptive efficacy, it does not carry the risk of teratogenesis associated with Accutane.

In conclusion, the risk of VTE with any combined hormonal contraceptives is increased over that of a non-pregnant, non-combined hormonal contraceptive user but is considerably lower than the risk of VTE in pregnancy and the postpartum period. Overall, the risk of VTE in users of these products is very low.
**Recommendations:**

1) The risk of VTE in CPA/EE users is very low and comparable to that of other combined hormonal contraceptives. For the majority of women, the benefits outweigh the risks.

2) Health-care providers should assess risk factors for VTE as one component of identifying the optimal choice of treatment for severe acne or other hyperandrogenism syndrome for a given woman.

3) Health-care providers should understand that the risk of VTE in CPA/EE users, as well as in combined hormonal contraceptive users, is highest in the first months of use, falling towards baseline thereafter.

4) Women should be counselled about the risk of VTE with any estrogen containing hormonal product and should be advised about signs and symptoms and what to do if these occur. To maintain perspective, it is useful to explain that the risk of VTE in pregnancy and the postpartum period is much higher than with CPA/EE use.

**References**