National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Obstetrics and gynaecology

Cyproterone and venous thromboembolism (VTE)

Objective: To make sense from the complex data and controversial recommendations around the use of newer progestins for contraception.

Safety data regarding venous thromboemboli: Adjusted rate ratios or odds ratios, of ethinyloestradiol (EE) preparation doses of 30-40 mcg, and the occurrence of VTE within the first year of use (for some studies) was reviewed. Data for the less commonly used norgestemate and desogestrel have not been included in this table.

Author	*Design*	*Period*	*VTE (n)*	*Non-users*	*Norethisterone*	*Levonorgestrel*	*Gestodene*	*Drospirenone*	*Cyproterone*
Lidegaard 2009[1]	cohort	1995 - 2005	2045	ref	2.8 (1.7-4.8)	1.9 (1.3-3.8)	4.4 (3.6-5.2)	7.9 (5.6-11.0)	6.7 (4.5-9.9)
Hylckama 2009[2]	case control	1999 - 2004	1524	ref	3.9 (1.4-10.6)	3.6 (2.9-4.6)	5.6 (3.7-8.4)	6.3 (2.9-13.7)	6.8 (4.7-10.0)
Lidegaard 2011[3]	historic cohort	2001 - 2009	1277	ref	2.2 (1.1-4.5)	3.1 (2.4-4.0)	6.2 (5.6-6.9)	6.4 (5.4-7.5)	6.3 (5.1-7.9)
Manzoli 2012[4]	meta-analysis	search to 2010	n/a	ref	no data	2.9 (2.3-3.7)	4.4 (2.6-7.5)	3.4 (1.9-6.2)	no data
Seaman 2004[5]	case control	1992 - 1998	25	n/a	ref	ref	no data	no data	1.4 (0.8-2.6)

From these studies there is a positive correlation between VTE and the dose of estrogen (≥50 mcg), age, BMI, smoking, thrombophilia, duration of use (highest in the 1st year), recent surgery, whether anticoagulation was confirmed or not, period of use (prior to 2001vs post-2001), cohort vs case-control studies, level of education, and whether the study was industry-funded.

Whatever the confounders, it seems that VTE occurs 3 times more frequently with levonorgestrel use within the first year compared with non-users. This risk increases to 6-fold with newer generation progestins.

In terms of absolute risks, the occurrence of VTE is small: it is 0.5 per 10 000 woman-years for non-pregnant non-users, vs. 1.5 for levornorgestrel, vs. 3 for cyproterone, vs. 6 per 10 000 woman-years for pregnant women.

Family planning: This may all be irrelevant, given the fact that we recommend levonorgestrel rather than the newer progestins such as cyproterone, for contraception in the PHC Family Planning chapter.

Hormone therapy: Cyproterone is given at a dose of 1 mg per day for 11 days instead of 2 mg per day for 21 days. Furthermore, the type of estrogen is different and the dose considerably higher (1-2 mg estradiol valerate vs. 35 mcg ethinyl estradiol).
What we already know from WHI data, is that conjugated equine estrogen (CEE) plus Medroxyprogesterone for HT increase the risk of VTE two-fold (HR 2.06; 95% CI 1.57-

2.70).[6] For women aged 50-59 years the 10-year adjusted risk of VTE is 1.4% vs. 6% at age 70-79 years.

In the CEE-only *vs*. placebo arm of the WHI study, the aHR for VTE was 1.05 (95% CI 0.84-1.31).[7] It appears that progestogen is a more important risk factor for VTE among HT users.

There is no available data on the risk of VTE with different progestins. Transdermal HT appears to confer a lower risk of VTE compared to oral formulations but high level quality evidence for this association is lacking.

Cost: Cyproterone (R30.90) ahead of medroxyprogesterone (R88.62) and norethisterone (R76.78) was selected, based on cost. Cyproterone has not been removed from the market by any of the regulatory authorities, rather the indications have been strengthened to include treatment of hirsutism and acne for young women.

Until clear data become available for different progestins on the risk of VTE, the recommendation of oral hormonal preparations for peri-menopausal women HT at PHC has been retained. Transdermal HT preparations may be considered if these formulations become affordable with a reduction in price.

References

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