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Update on oral contraceptives and venous thromboembolism

It is generally accepted that there is an increased risk of venous thromboembolism (VTE) in current users of combined oral contraceptives (COC). The influence of specific types of COC on the risk of thrombotic events remains the most important safety issue for these products, and has been the subject of safety reviews including a recent review, which was published in an Irish Medicines Board newsletter in June 2011 <http://www.imb.ie/images/uploaded/documents/Drug%20Safety%20Newsletter%2042%20-%20final%20-%20June%202011.pdf>. More recently, a Danish observational study was published which assessed the effect of different types of COC, according to

progestogen type and oestrogen dose, on the risk of VTE (**BMJ 2011;343:d6423**).

This cohort study collected data on women aged 15-49 years from 2001-2009 (n=1,436,130) from four national registries; Statistics of Denmark, the national registry of patients, the national causes of death registry and the national registry of medicinal products. The study focused on the period following the launch of the COC containing drospirenone in 2001; to account for COC use before the start of the study, the use of COC from 1995 was also assessed. Exclusion criteria for the study included women with previous recorded thrombosis, cancer (including gynaecological, abdominal organs, breast, lung or haematological), those who were pregnant or who underwent hysterectomy or sterilisation and those with diagnosed coagulation disorders. A total of 1,296,120 women, who fitted the criteria, were included in the statistical analysis (equivalent to 8,010,290 women years of observation). First episodes of VTE were identified from hospital records, and events that were treated with anticoagulants for at least 4 weeks were defined as confirmed VTE. Results showed that of the 4246 first time VTE which were included in the analysis, 2847 (61%) were confirmed VTE.

The study showed that **the overall incidence rate of VTE in non-users of COC was 3.7 per 10,000 women years.**

After adjustment for age, calendar year and education, **the relative risk of confirmed VTE in current users of COC compared with non-users was:**

- 2.92 (95% CI 2.23-3.81) for levonorgestrel and 30-40 µg ethinylestradiol (EE) preparations
- 3.09 (2.41-3.97) for levonorgestrel and 30-40 µg EE phasic preparations
- 6.61 (5.6-7.8) for desogestrel, 6.24 (5.61-6.95) for gestodene and 6.37 (5.43-7.47) for drospirenone with 30 µg EE preparations

Preparations with a newer progestogen and 20 µg EE did not have a significantly lower risk of VTE than those with the same progestogen and 30 µg of EE. The relative risk of confirmed VTE for users of EE and cyproterone was 6.35 (5.09-7.93). Progestogen only products were associated with no increased risk of VTE, whether taken as low dose norethisterone pills, as desogestrel only pills or in the form of hormone releasing intrauterine devices.

There were some limitations to the study including a lack of information on confounders such as family history of VTE and body mass index (BMI). The authors concluded that compared with non-users of hormonal contraception, current users of COC with levonorgestrel had a threefold increased risk of VTE and those using COC with desogestrel, gestodene, drospirenone, or cyproterone a six to sevenfold increased risk. After adjusting for length of use, **users of COC with desogestrel, gestodene or drospirenone were at twice the risk of VTE compared with users of COCs containing levonorgestrel.**

An accompanying editorial (**BMJ 2011;343:d6592**) reviewed the study and advised that it is difficult not to conclude that use of COC with desogestrel, gestodene or drospirenone confers a higher risk of VTE than those with levonorgestrel and that many clinicians will choose to minimise the risk by prescribing a COC with levonorgestrel whenever possible. The editorial however also advises that **it is crucial not to exaggerate the risk, in that COC are remarkably safe and may confer important long-term benefits in relation to cancer and mortality.** The risk of VTE is probably greater during the first few months of use, before falling to a level that remains above that of non-users until the use of these contraceptives is stopped, when the excess risk rapidly disappears.



Female smokers more likely to get heart disease! It is estimated that there are 1.1 billion smokers in the world, of whom a fifth are women. Each year, >5 million deaths occur that are directly attributed to tobacco, of which 1.5 million occur in women. It is now accepted that female smokers have a significantly greater relative risk of lung cancer than do male smokers but there is some debate about whether this sex difference is also true for smoking and coronary heart disease (CHD). A recent study aimed to estimate the effect of smoking on CHD for women compared with men (*Lancet 2011; 378: 1297-305*). A

total of 26 articles, containing information on smoking and CHD for >3 million individuals from developed and developing countries (follow-up from 5 - 40 years) were reviewed to examine the association between smoking and CHD. Overall results (adjusted for age) showed an 11% increased relative risk for CHD in female smokers compared with male smokers. **When adjusted for other cardiovascular risk factors (including blood pressure, total cholesterol, diabetes and BMI) the results showed an increased relative risk of 25% for female smokers versus male smokers.** Of interest, the relative risk appeared to increase by 2% for each extra year of study follow-up for women. There was no clear evidence that the sex differential was either attenuated or strengthened with increasing age. Nor was there evidence of a sex difference in risk between those who were former smokers and those who had never smoked. There were limitations to the study, including lack of standardisation of the number of cigarettes and duration of smoking history between the pooled studies. Moreover, the authors were unable to adjust for the rates of use of oral contraceptives (COC), which are known to be associated with an increased risk of CHD in women smokers. However, the results of the findings were consistent across all ethnic regions, including Asia, where the rate of COC use is very small. In addition, the cohort of patients included in the study was very large and the results were consistent across regions and between studies. The authors note that the popularity of smoking for young women in some low-income and middle-income countries might be on the rise, therefore they suggest that these findings suggest that **inclusion of a female perspective in tobacco-control policies is crucial.**



Drug-induced photosensitivity Photo-induced drug eruptions (PIDEs), which occur following exposure to a drug (either topically or systemically) and either ultraviolet (UV) or visible radiation, represent 8% of reported cutaneous adverse drug reactions. The diagnosis, prevention and management of PIDEs was recently reviewed (*Drug Safety 2011;34(10):821-837*). PIDEs can be classified as photoallergic drug reactions (PADR) or phototoxic drug reactions (PTDR) based on their mechanism of action; however clinically the distinction can be difficult to make.

Diagnosis is largely based on a detailed clinical history and physical examination. Special attention should be given to the temporal relationship of the eruption and

starting a new medicine, and screening for diseases associated with photosensitivity (e.g. systemic lupus erythematosus) should be included in the assessment. On physical examination, a photodistributed eruption involving the face, the V of the neck, forearms and hands, (with sparing of the non sun-exposed sites in particular 'doubly covered areas' such as the genital area and breasts) is expected. PIDEs can take many different forms; PADR classically present as a predominantly eczematous eruption while PTDR which are more common than PADR, present as exaggerated sunburn with associated burning and itching sensations. Other manifestations include lichenoid eruptions, onycholysis, erythema multiforme, hyperpigmentation and telangiectasia. Phototesting and photopatch testing may be used to help the diagnosis. A large number of medications have been implicated in the literature, however in the opinion of the authors of the review, the most common photosensitizing drugs are **amiodarone, chlorpromazine, doxycycline, hydrochlorothiazide, nalidixic acid, naproxen, piroxicam, tetracycline, thioridazine and voriconazole.** Management of a PIDE initially involves the diagnosis of photosensitivity and identification of the possible offending drug. The next step may involve discontinuation of the drug, which in most cases results in abatement of the photosensitivity shortly after discontinuing the drug. Other measures that may be required include the use of topical or systemic corticosteroids depending on the severity of the eruption. Discontinuation may not be possible for all patients and in these cases secondary preventive measures such as avoidance of exposure to sunlight and the use of protective clothing and broad spectrum sunscreen should be implemented. Another strategy which has been suggested is the administration of medications in the evening rather than during the daytime, however the appropriateness of this strategy must be assessed on a drug-to-drug basis. Primary prevention is also an important aspect of management and physicians should counsel patients about sun avoidance and protection when they initiate treatment with a known photosensitizing medication.