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EPIDEMIOLOGY OF ORAL CONTRACEPTIVE RELATED THROMBOSIS

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Oral contraceptives have been available since the 1960s and are now used by more than 100 million women throughout the world (1). The effects of oral contraceptives continue to be of immense interest, because oral contraceptives are the most frequently and very often long-term used drugs by healthy women in the developed world.

Unfortunately, there is no recognised classification system of oral contraceptives based on their pharmacological properties. One system used is that the progestogens are classified as first, second, third and fourth generation. The first generation includes: ethynodiolacetate, lynestrenol, norethisterone (acetate) and norethynodrel. The second generation includes: norgestrel, levonorgestrel and norgestrione. The third generation includes: desogestrel, gestodene and norgestimate. The fourth generation includes: chlormadione and cyproterone acetate (both C21 derivatives). A miscellaneous group includes mainly C21 steroids, such as dydrogesterone, medrogestone, medroxyprogesterone acetate and the natural progesterone. In currently available oral contraceptives ethinyl estradiol in the amount of 20, 30, 35 or 50 μg is combined in several ways with the different progestogens, either mono-, bi or triphasic, and in various dosages (2–5).

Besides having beneficial effects, the highly effective protection against pregnancy, like all medicines, oral contraceptives also show adverse effects. Even a small increase in risk will affect a large number of women, who are often young and healthy. Ever since oral contraceptives have been marketed, reports have appeared on links between oral contraceptive use and cardiovascular disease, including both venous and arterial thrombosis (6–8). Oral contraceptives influence the hemostatic-, carbohydrate-, lipid-, and endothelium systems, mechanisms regulating blood pressure and probably as yet unknown systems, as a result of which there is an increased risk of cardiovascular disease (9–16). In venous as well in arterial thrombosis, the final event leading to the disease will be clot formation, nevertheless the risk factors are different (Tables 1 and 2).

Cardiovascular side effects can be distinguished in venous thrombosis (deep-vein thrombosis, pulmonary embolism, ischaemic stroke) and arterial thrombosis (acute myocardial infarction, ischaemic stroke, hemorrhagic stroke and peripheral arterial occlusive disease).

Venous thrombosis

Venous thrombosis is a multicausal disease, in which several risk factors (acquired or genetic) need to be present simultaneously. The risk of thrombosis rises sharply with the number of risk factors. Since age is a strong risk factor for thrombosis, the number of risk factors required for thrombosis decreases with age (17).

The incidence of venous thrombosis in young women in the fertile age is low and depends on predisposing factors such as pregnancy, oral contraceptive use, hormone replacement therapy, use of hormones during in vitro fertilisation treatment and ovulation induction, carrier ship of a coagulation defect or combinations of risk factors.

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Oral contraceptives and venous thrombosis

After the first case report by Jordan of a nurse who developed pulmonary embolism after oral contraceptives as a treatment for endometriosis (18), many studies were conducted on the association between oral contraceptive use and venous thrombosis, and on the effects of oral contraceptives on the haemostatic system (procoagulation, anticoagulation and fibrinolysis). Epidemiological studies (cohort- and case-control studies) showed that oral contraceptive use was a clear risk factor for venous thrombosis (three- to fourfold increased risk) and studies with healthy volunteers (randomised and cross-sectional studies) showed that oral contraceptives alter various haemostatic variables, inducing a slight tilt towards a prothrombotic state (19). In order to reduce the cardiovascular risk during oral contraceptive use, the oestrogen type was changed from mestranol into ethinyl oestradiol and the oestrogen content was lowered from 100 to 50 μg ethinyl oestradiol and subsequently less. The decrease from 100 to 50 μg seemed effective in decreasing the risk of arterial and venous disease. Nevertheless, the lowering of the oestrogen content to less than 50 μg ethinyl oestradiol and the efforts to produce newer types of progestogens with purpose of reduction of the risk of thrombotic disease did not lead to the expected further decrease in the incidence of venous thrombosis (19–22).

In 1995, several studies showed that the newer "third generation" oral contraceptives which contained desogestrel or gestodene as progestogens had higher risks of venous thrombosis than the older "second generation" oral contraceptives which contained mainly levonorgestrel (21,23–25). Subsequent studies had variable results (26–33). The original studies were heavily criticised, and it was hypothesised that the observed higher risk for oral contraceptives containing desogestrel or gestodene was completely explained by bias and confounding.

From several papers and a recent meta-analyses it can be concluded that low dose oral contraceptives with a third generation progestogen confer a higher risk (by a factor 1.5–1.8) of venous thrombosis than the previous generation of oral contraceptives (34,35). These differences in risk appear to be real and cannot be accounted for by methodologic problems in the studies or the analyses (19). For the venous thrombosis risk of preparations containing the newer progestogens as cyproterone acetate and drospirenone, we have to await the results of ongoing large observational studies.

It is unknown what the chances are to develop a recurrent venous thrombosis once a woman developed venous thrombosis during oral contraceptive use and either continues or discontinues using oral contraceptives. Nevertheless, logical reasoning along the lines that venous thrombosis is a multicausal disease would imply that the less risk factors exist, the smaller the risk of recurrence. This agrees with the recommendations of the World Health Organisation to discontinue or not to start using oral contraceptives if a woman has a personal history of venous thrombosis (36).

The risk for venous thrombosis is highest during initial oral contraceptive use. This suggests a subgroup of women who are at immediate risk of thrombosis when exposed to oral contraceptives. In a case control study (37) it was concluded that women with inherited clotting defects who use oral contraceptives develop venous thrombosis not only more often, but also sooner. Therefore venous thrombosis in the first year of oral contraceptive use may indicate the presence of an inherited clotting defect.

Susceptibility to prothrombotic states

In 1994, the first interaction between an inherited coagulation disorder and oral contraceptive use was described (38). In non-carriers who use oral contraceptives, the risk of venous thrombosis was increased fourfold, in carrier non-users the risk was increased eightfold, and in users of oral contraceptives who also carried the factor V Leiden mutation the risk rose 30–50-fold. This susceptibility has been confirmed in other studies (39,40) and is even higher in the few women who are homozygous for factor V Leiden (41). The risk of carriers using a desogestrel (third generation)-containing oral contraceptive as compared with non-carriers non-users was found to be increased almost 50-fold (21).

Other inherited coagulation defects (protein C-, protein S-, antithrombin deficiency, high factor VIII plasma levels and prothrombin mutation) also appear to synergistically lead to an excess risk of venous thrombosis among oral contraceptive users. Although the prevalence of protein C, protein S or antithrombin deficiencies is estimated at less than 1%, factor V Leiden and prothrombin 20210A are common (2–6%) (42–47).

Arterial disease

After the introduction of oral contraceptives in the 1960s, myocardial infarction and ischaemic