Karolinska Institutet

Department of Woman and Child Health
Karolinska Institutet, Stockholm, Sweden

Effects of combined oral contraceptives on hemostasis and biochemical risk indicators for venous thromboembolism and atherothrombosis

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Skandiasalen, Astrid Lindgrens Barnsjukhus Karolinska Universitetssjukhuset Solna,

Fredagen den 30 mars, 2007, kl 09.00.

av

Marianne van Rooijen

Leg. Läkare

Huvudhandledare
Doc Katarina Bremme
Institutionen för Kvinnors och Barns hälsa
Karolinska Institutet

Bihandledare
Professor Anders Hamsten
Enheten för aterosklerosforskning
Institutionen för medicin – Solna
Karolinska Institutet

Fakultetsopponent
Professor Per Morten Sandset
Medisinske fakultet
Universitetet i Oslo

Betygsnämnd
Professor Erik Berntorp
Institutionen för kliniska vetenskaper,
Malmö Lunds Universitet

Docent Jan Svensson
Institutionen för kliniska vetenskaper
Karolinska Institutet

Docent Helle Kieler
Kvinnors och Barns Hälsa
Uppsala Universitet

Stockholm 2007

Abstract

Combined oral contraceptives (COCs) are one of the most common contraceptive methods in the world. Already a few years after their introduction, in the early 1960s, case reports were published showing associations between use of COCs and venous and arterial thromboembolism. Epidemiological studies have confirmed increased risk for these unwanted side effects, but the mechanisms behind the increase are still not fully evaluated.

The overarching aim of this thesis was to identify alterations in hemostasis as well as in established and novel risk markers for venous thromboembolism and atherothrombotic disease during treatment with COCs containing different types and doses of progestogen and estrogen.

In a prospective randomized cross-over study (papers I-III), two different monophasic low-dose COCs (one second-generation COC and one third-generation COC) were used for two two-month periods with a two-month wash-out period in between. Changes in hemostatic factors, lipoproteins and other risk indicators for atherothrombosis were examined before and during treatments. Changes in hemostatic factors occurred during both treatments towards a more hypercoagulable state, and were more pronounced with the third-generation COC than with the second. The observed alterations in serum cholesterol were more advantageous in women using third-generation COCs, but conversely the C-reactive protein (CRP) levels were enhanced more than during use of the second-generation COC. Other inflammatory markers investigated did not indicate occurrence of a general inflammatory response during use of COCs. A positive correlation between circulating levels of coagulation factor VII and triglycerides in COC users was also observed, with higher concentrations of both during use of third-generation COCs. In addition, users of COCs showed a significantly reduced sensitivity to the anticoagulant effect of activated protein C (APC), a well established risk factor for venous thrombosis, and this effect strongly correlated with changes in the circulating levels of sex-hormone binding globulin (SHBG). In study two (paper IV), 11 women used two kinds of emergency contraceptives (EC), one containing progestogen alone and one containing both progestogen and estrogen. Biochemical risk indicators were examined before and at frequent intervals after treatment. Already two hours after treatment, the plasma concentrations of some coagulation parameters differ from baseline concentrations, regardless of treatment. Increases in plasma concentrations of fibrinogen and prothrombin fragment 1+2 and decrease in antithrombin were observed. In the last study (paper V), APC resistance, measured by two methods with different sensitivities towards sex hormones, was evaluated in the luteal and follicular phases of the menstrual cycle. No differences in APC resistance between follicular and luteal phase were observed, even though the serum estrogen levels increased 200%.

In conclusion, although third generation COCs were developed to reduce the negative effects on lipoproteins and the associated risk of atherothrombosis with older COC preparations, their use may affect other risk indicators in a less advantageous direction. The raised serum CRP concentration during treatment with COCs appears to be related to a direct effect on hepatocyte CRP synthesis. SHBG is a potential surrogate marker for the prothrombotic risk state induced by different OC preparations. Even a very short exposure to rather high levels of exogenous sex hormones causes a prompt effect on hepatic protein synthesis and induces a rapid activation of hemostasis. However, the physiological increase in estradiol during the normal menstrual cycle is not large enough to affect the individual's sensitivity to APC.

Key words: Combined oral contraceptives, emergency contraception, menstrual cycle, ethinylestradiol, levonorgestrel, desogestrel, lipoproteins, hemostasis, risk indicators, APC resistance, SHBG

ISBN 978-91-7357-089-3