Risk of pulmonary embolism, ischaemic stroke and myocardial infarction in women using combined oral contraceptives in France: a cohort study on 4 million women aged 15 to 49 years based on SNIIRAM and PMSI data

Synopsis

Background

France presents an extensive contraceptive coverage, composed of 80% of prescription-only methods with a marked predominance of oral hormonal contraception. Many large-scale studies published in the international scientific literature concordantly demonstrate that combined oral contraception is associated with an excess risk of venous thromboembolic and arterial ischaemic events. Many authors and institutions all over the world recommend combined oral contraception (COC) with so-called second-generation preparations containing a progestin such as levonorgestrel and low-dose ethinylestradiol (EE). However, the amplitude of the excess venous and arterial thromboembolic risk associated with other third- or fourth-generation preparations with various doses of EE remains highly controversial.

The objective of this study, conducted at the request of French health authorities, was to determine the absolute and relative risks of serious events such as pulmonary embolism, ischaemic stroke and myocardial infarction associated with first-, second- and third-generation COCs. This analysis also concerned the type of progestin and the dose of EE. This study was designed to guide health authorities and healthcare professionals by providing an estimate of venous and arterial thromboembolic risks of COC under real use conditions in France, in order to improve the individual and community oral contraception prescription strategy. The study protocol was elaborated by the Public Health Studies Department of the *Caisse nationale de l'assurance maladie des travailleurs salariés* (CNAMTS) [French National Health Insurance Fund for Salaried Workers] in collaboration with the Epidemiology Pole of the *Agence nationale de sécurité du médicament et des produits de santé* (ANSM) [French

National Agency for Medicines and Health Products Safety]. Data processing and preparation of the report were performed by CNAMTS.

Method

This historical cohort included all women aged 15-49 years, living in France, with at least one COC reimbursement between 1st July 2010 and 31st December 2011 identified in the French national health insurance system (SNIIRAM) database. Women with a history of cancer or venous or arterial thromboembolism were excluded.

Endpoints were the incidence rates of pulmonary embolism, ischaemic stroke, myocardial infarction, and a composite endpoint comprising PE, stroke and MI. Events of interest were identified, after linking with the SNIIRAM, in the PMSI database which records information on all hospitalisations in France. Data were analysed by using Poisson regression as the main model for calculation of the relative risk. Confounding variables used for adjustments in multivariate analysis were age, complementary Universal Health Insurance cover (CMUc), corresponding to the poorest 12% of the population, a social disadvantage score, diabetes, HT, medically managed smoking, follow-up by a private gynaecologist, EE dose (for comparisons between progestins) and the progestin (for comparisons between EE doses).

Results

This study included 4,343,692 women with a mean age of 28.0 years (standard deviation: 8.7 years), corresponding to 2,972,857 person-years of COC exposure, i.e. an average of 8.2 months per person. 69.2% of the women included in the study had been exposed to a first/second-generation COC, 27.2% to a third-generation COC (reimbursed) and 3.6% of women had alternately received a first/second-generation COC and a third-generation COC.

Women reimbursed for a third-generation COC were significantly younger (15-19 years: 20.7% versus 18.1% for G1/G2 COC), more economically advantaged

(CMUc 7.8% versus 13.9%), with a lower cardiovascular risk (diabetes, treated HT, smoking), less often following a pregnancy (8.6% versus 10.1%) and more often followed by a gynaecologist (33.5% versus 28.7%). The dose of ethinylestradiol (EE) associated was significantly lower for third-generation COCs (20 µg: 57.1% of women reimbursed for a G3 COC versus 16.8% for G1/G2 COCs - 30-40 µg: 48.3% of women reimbursed for a G3 COC versus 85.4% for G1/G2 COCs).

Pulmonary embolism risk

During follow-up of the cohort, 991 women of the cohort were hospitalised for pulmonary embolism (absolute risk of 33 per 100,000 person-years). The adjusted relative risk (RRa) of pulmonary embolism was twofold higher with G3 COC than with G2 COC: RRa = 2.04 (95%CI: 1.76 to 2.37). Analysis by EE dose showed a significantly lower pulmonary embolism risk for the 20 µg dose: RRa = 0.73 (95%CI: 0.61; 0.86] compared to the reference dose of 30/40 µg. After adjustment for EE dose, desogestrel (G3 COC) and gestodene (G3 COC) were associated with a significantly pulmonary embolism risk (reference levonorgestrel = 1) of 2.14 [95%CI: 1.83 to 2.49] and 1.56 (95%CI: 1.13 to 2.09), respectively.

Analysis by progestin and EE dose (reference levonorgestrel 30/40 µg = 1) showed that two combinations were associated with a significantly lower RRa: norethisterone 35 µg: RRa = 0.41 (95%CI: 0.18 to 0.76) and levonorgestrel 20 µg: RRa = 0.74 (95%CI: 0.54 to 0.98). Three combinations were associated with a significantly higher risk: norgestrel 50 µg: RRa = 1.81 (95%CI: 1.06 to 2.88), desogestrel 20 µg: RRa = 1.53 (95%CI: 1.27 to 1.83) and desogestrel 30/40 µg: RRa = 2.19 (95%CI: 1.84 to 2.61).

After adjustment for all other variables, an excess risk of pulmonary embolism was observed for women covered by CMUc (1.5-fold) and for older women (45-49 years) with a fourfold higher risk than for women aged 15 to 19 years.

Arterial ischaemic risk

During follow-up of the cohort, 500 women were hospitalised for ischaemic stroke and 226 women were hospitalised for myocardial infarction (MI), i.e. an absolute risk of 17 and 8 per 100,000 person-years, respectively. The adjusted relative risk of ischaemic stroke and MI of G3 COC compared to G2 COC was not

significantly different. In contrast, analysis by EE dose showed a significantly lower risk of MI for the 20 µg dose compared to the 30/40 µg dose: RRa = 0.61 (95%CI: 0.36 to 0.98]. The RRa of ischaemic stroke for the 20 µg dose was not significantly lower than that of the 30/40 µg dose: RRa = 0.93 (95%CI: 0.70 to 1.21). Analysis by progestin and EE dose (reference levonorgestrel 30/40 µg = 1) showed that one combination was associated with a significantly higher RR: norgestrel 50 µg: RRa = 2.62 (95%CI: 1.52 to 4.17) for ischaemic stroke and RRa = 3.01 (95%CI: 2.06 to 4.25) for myocardial infarction.

After adjustment for all other variables, the risk of ischaemic stroke and MI was increased 22-fold and 81-fold, respectively, between the youngest group and the 45-49 years age- group. Women covered by CMUc had a 1.5-fold higher risk of ischaemic stroke and a 2.4-fold higher risk of MI. The influence of cardiovascular risk factors (diabetes, HT and smoking) was more marked for MI (3.0; 2.1; 5.2) than for ischaemic stroke (1.8; 2.0; 1.5).

Analysis of the composite endpoint (PE/stroke/MI)

During follow-up, 1,717 women were hospitalised for the composite endpoint (991 PE, 500 strokes and 226 MI), i.e. an absolute risk of 58 per 100,000 person-years. The adjusted relative risk (RRa) of composite events associated with G3 COC compared to G2 COC was increased by 52%: RRa = 1.52 (95%CI: 1.34 to 1.72). Analysis by EE dose showed a significantly lower risk for the 20 µg dose compared to the reference dose of 30/40 µg: RRa = 0.75 (95%CI: 0.66 to 0.86).

Sensitivity analyses

All of the sensitivity analyses performed confirmed the trends of the main analyses, especially the excess risk of pulmonary embolism associated with G3 COC compared to G2 COC in the context of post-partum prescriptions: RRa = 1.64 (95%CI: 1.02 to 2.59).

Conclusion

This study reports similar results to those of the most recent and most powerful international observational studies, despite the limitations inherent to the use of databases combining administrative and medical information. Analysis of this cohort of more than 4 million women living in France receiving reimbursements for COC confirmed the twofold higher risk of pulmonary embolism associated with third-generation COCs compared to second-generation COCs, as the risk of pulmonary embolism increased from 25 to 50 per 100,000 person-years between G2 COC and G3 COC. These results, based on French data, provide new insight into the role of the EE dose. The 30/40 µg EE dose compared to the 20 µg dose was associated with a 37% increase of the pulmonary embolism risk as well as a 64% increase of the myocardial infarction risk.

Overall, these results show that old generation progestins, such as levonorgestrel (G2 COC), combined with 20 µg of ethinylestradiol, were associated with lower venous and arterial thromboembolic risks. This combination of 100 µg of levonorgestrel and 20 µg of ethinylestradiol has been marketed and reimbursed in France since April 2010[1].

Key-Words: *combined oral contraceptive, pulmonary embolism, ischaemic stroke, myocardial infarction, cohort, SNIIRAM, PMSI.*

[1] Marketed under the brand names of Leeloo®, Lovalulo® and Optilova® since 14/4/2010, 6/11/2010 and 16/8/2012, respectively (65% reimbursement).