

FORUM

Contraceptive pills and thrombosis: effects of the French crisis on prescriptions and consequences for medicine agencies

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Summary. The higher risk of venous thromboembolism with 3rd and 4th- generations combined oral contraceptives compared to 2nd generation triggered a media crisis in France. Exposure to 3rd or 4th-generation combined oral contraceptives led to an annual excess of around 100 premature deaths in Europe. In the absence of any demonstrated additional benefit of these combined oral contraceptives, measures were taken to decrease exposure of women to this illegitimate excess of risk. As a consequence, this crisis saw a 45% decrease in the prescription of 3rd and 4th-generations combined oral contraceptives, without adverse consequences.

Keywords: adverse drug reactions; contraceptives; public health; pulmonary embolism; thrombosis.

Introduction

In December 2012 a patient sued the German pharmaceutical company Bayer and the French medicine agency ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé), after she had a stroke while taking a third-generation combined oral contraceptive (COC). Following this a large media crisis took place in France, about the use of COCs [1]. In this context, in January 2013, the French medicine agency asked for a Europe-wide change in the summary of product characteristics (SmPC) of ‘third and fourth-generation’ COCs, because of their known higher risk of venous thromboembolism (VTE), and proposed restraining their use to ‘second line’ if intolerance to

‘first or second-generation’ COCs was observed (under the scope of Article 31 of European Directive 2001/83/EC) [2].

Since their introduction in the 1960s, an increased risk of VTE was associated with COCs: a three-fold to six-fold risk of venous thrombosis is reported in epidemiological studies [3,4]. The absolute risk, however, remains low, with a baseline risk of about two cases per 10 000 woman-years, which may be increased to 12 cases per 10 000 woman-years in COC-users (<http://www.ema.europa.eu>). In order to try to lower this risk the dose of ethinylestradiol has been reduced from 100 µg to below 50 µg. Different progestogens have also been designed over the years, with the intention of reducing the cardiovascular impact (leading to the controversial concept of ‘generations’). The ‘second-generation’ COCs contain levonorgestrel, the ‘third-generation’ COCs contain gestodene or desogestrel and more recent COCs contain drospirenone (‘fourth generation’). The higher risk of VTE with ‘third and fourth-generation’ COCs compared with ‘second-generation’ COCs has been known since 1995 and 2001, respectively [5]. Roughly, the safest COC (containing levonorgestrel) increased the risk of VTE 3-fold, whereas gestodene, desogestrel or drospirenone-containing COCs double this risk compared with levonorgestrel-containing COCs. Some argue that these data are controversial and questionable but after dissection of potential confounding data have confirmed the strength of this increased risk. The main difference between studies that demonstrated an increased risk and those that did not were the source of funding: public or by the manufacturers, respectively [6]. Furthermore, laboratory methods demonstrate a more pronounced activated protein C resistance test and levels of sex hormone binding globulin (markers of thrombogenicity) for these COCs compared with second-generation COCs [7]. Recent data demonstrate also an increased risk of arterial thrombosis with COCs by a factor of 0.9–2.3, the lower risk being observed with COCs that contain a very low dose of ethinylestradiol (20 µg) [8]. Concerning arterial thrombo-

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sis and the progestogen content of COC, relatively small differences in risk are observed [8].

At least 10 million American women and 100 million women worldwide are using a COC [9]. As in other European countries, COCs remain the most widely used birth control method in France. In 2011, about 4.3 million French women were exposed each day and half of them used a third or fourth-generation COC. Each year, around 2500 VTEs, among which there are 850 cases of pulmonary embolism and 20 subsequent deaths, are attributable in France to the use of COCs [10]. As compared with the use of first and second-generation COCs, exposure to third or fourth-generation COCs led to an annual excess of 1150 VTE events and nine premature deaths [10]. Such a crude analysis can be taken to a larger European level (France, Germany, Italy, Spain and the UK) by applying the same risk appreciation and taking into account their respective levels of exposure to third and fourth-generation contraceptives, estimated from sales data. Overall, in these five countries, which account for approximately 60% of European Union inhabitants, exposure in 2011 to third and fourth-generation contraceptives led to a yearly excess of 7700 VTE events and 60 premature deaths due to pulmonary embolism, as compared with the use of a second-generation COC. For this reason, and in the absence of any demonstrated additional benefit concerning their tolerance and safety, it is of paramount importance to take measures to decrease exposure of women to this illegitimate excess risk. When COC prescription is considered, the best strategy is to use the safest one with regard to VTE risk (i.e. the one that contains the lowest tolerable dose of ethinylestradiol together with the second-generation progestogen, levonorgestrel [4,8] (norethisterone or norgestimate-containing COCs may also be prescribed, as their risk of VTE seems to be similar to lenonorgestrel-containing COCs).

Despite several national recommendations and guidelines since 1995, concerning the initiation of oral contraception, prescription of third and fourth-generation COCs has increased. Under European rules countries must accept drugs that are approved by the European Commission, but this does not prevent national authorities making recommendations on how the drugs should be used [2]. National authorities are also allowed to suspend drugs from their market temporarily but cannot ban them. France's health ministry had announced that the social security system will no longer reimburse third-generation COCs from 31 March 2013; nevertheless, some of the most recent pills had already not been reimbursed but this did not prevent their use, demonstrating that it is not a sufficient enough safety measure. This problem of safety of third and fourth-generation COCs is not limited to France or Europe, as in the United States Bayer has paid out compensation after nearly 3500 legal claims that its fourth-generation COC Yasmin caused VTE.

This crisis has provoked major alarm among French women, prescribers and the media, with the risk of reckless withdrawal of contraception and thus of a potential increased number of unwanted pregnancies within the following months. An important attempt to communicate with women was undertaken through periodic publication of factual information on the French Medicinal Agency website, along with periodic media interventions. A major and rapid switch of contraceptive methods was observed in France from December 2012 (before the crisis) to January 2014. If COC use slightly decreased by 5.1%, a major change was observed with a switch in the prescription of COC; that is, a 45% decrease in the sale of third and fourth-generation COCs while the sale of second-generation COCs increased by 30%, with a more marked increase in the sale of COCs with the lowest dosage of ethinylestradiol. Interestingly, an increase of 47% in the use of intra-uterine devices was also observed as well as a minor increase in emergency contraceptive use (4.4%). Concerning abortion, no increase was observed when we compared the incidence with the similar period of the previous years (data from the French Ministry of Health). These data should also be confirmed and put into perspective when comparing the number of births from the last trimester of 2013–2014.

The Article 31 referral held at the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medical Agency, did not retain the French proposal to restrain the prescription of third and fourth-generation COCs, with a higher risk of VTE, in second line. Instead, the PRAC clearly reinforce safety measures before the prescription of a COC. The summary of product characteristics (SmPC) now states that 'the decision to prescribe a COC should take into consideration the individual woman's current risk factors, particularly those for VTE, and how the risk of VTE with the chosen COC compares with other COCs'. This referral also updated the absolute risk of VTE associated with COCs, which is slightly higher than previously indicated in the SmPC. These proposals also took into consideration the voice of the patients' association of women victims of pulmonary embolism. Finally, competent national authorities must also reinforce follow-up measures on the implementation of their guidelines, as clear and repeated recommendations from European and national authorities have not precluded a much larger than expected use of third and fourth-generation COCs. National authorities in France will also regularly survey the sales of third and fourth-generation COCs during the upcoming years and will reinforce safety measures in the case of any increase in their prescriptions.

Disclosure of Conflict of Interest

The authors state that they have no conflicts of interest.

References

- 1 Arie S. French doctors are told to restrict use of third and fourth generation oral contraceptives. *BMJ* 2013; **346**: f121.
- 2 Arie S. European agency defends existing advice on later generation contraceptive pills. *BMJ* 2013; **346**: f279.
- 3 Stegeman BH, De Bastos M, Rosendaal FR, van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, Dekkers OM. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ* 2013; **347**: f5298.
- 4 Helmerhorst FM, Rosendaal FR. Is an EMA review on hormonal contraception and thrombosis needed? *BMJ* 2013; **346**: f1464.
- 5 Vandenbroucke JP, Rosing J, Bloemenkamp KWM, Middeldorp S, Helmerhorst FM, Bouma BN, Rosendaal FR. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med* 2001; **344**: 1527–35.
- 6 Vandenbroucke JP, Helmerhorst FM, Rosendaal FR. Competing interests and controversy about third generation oral contraceptives. *BMJ* 2000; **320**: 381–2.
- 7 Tans G, Bouma BN, Büller HR, Rosing J. Changes of hemostatic variables during oral contraceptive use. *Semin Vasc Med* 2003; **3**: 61–8.
- 8 Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012; **366**: 2257–66.
- 9 Petitti DB. Combination estrogen-progestin oral contraceptives. *N Engl J Med* 2003; **349**: 1443–50.
- 10 Tricotel A, Raguideau F, Collin C, Zureik M. Estimate of venous thromboembolism and related-deaths attributable to the use of combined oral contraceptives in France. *PLoS One* 2014; **9**: e93792.