Expert Review of Obstetrics & Gynecology

ISSN: 1747-4108 (Print) 1747-4116 (Online) Journal homepage: informahealthcare.com/journals/ierb20

Combined oral contraceptive pill and venous thromboembolism

Anne Szarewski

To cite this article: Anne Szarewski (2011) Combined oral contraceptive pill and venous thromboembolism, Expert Review of Obstetrics & Gynecology, 6:5, 473-476, DOI: 10.1586/eog.11.52

To link to this article: https://doi.org/10.1586/eog.11.52

Published online: 10 Jan 2014.

www.expert-reviews.com/toc/eog/6/5

Combined oral contraceptive pill and venous thromboembolism

Expert Rev. Obstet. Gynecol. 6(5), 473–476 (2011)

Anne Szarewski

Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary, University of London, Charterhouse Square, London, EC1M 6BQ, UK
Tel.: +44 207 882 3508
Fax: +44 207 882 3890
a.szarewski@qmul.ac.uk

"...the prescribing of combined oral contraceptive pills to women with a body mass index >30 kg/m², and particularly those with multiple risk factors for cardiovascular disease, is becoming difficult to justify."

An increased risk of venous thromboembolism (VTE) was the first serious side effect identified with the combined oral contraceptive pill (COC) in the 1960s. This was quickly realised to be due to the estrogen content of the COC and this has been the main driver behind reductions in estrogen dose seen in the last 50 years [1]. However, in 1995, several studies were published that suggested that COCs containing the progestogens desogestrel and gestodene ('third-generation' COCs) increased the risk of VTE more than 'second-generation' COCs (containing levonorgestrel). This created a widespread pill-scare, which has never fully been resolved, despite the incongruity that progestogen-only contraceptives do not increase VTE risk and newer evidence showing that prescriber bias and many confounding factors were not taken into account [2].

"The European Active Surveillance Study on Oral Contraceptives ... suggests all venous thromboembolism rates are higher than previously thought."

Since the publication of those studies, BMI of over 30 and smoking have emerged as significant risk factors for VTE in women on the COC [1]. The Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for venous thrombosis found that women who used COCs and had a BMI ≥30 kg/m² were at a 24-fold greater risk of VTE compared with women who did not use oral contraceptives and had a normal BMI of <25 kg/m [3]. Another analysis from the MEGA study found that smokers who used COCs had a ninefold increase in VTE risk compared with nonsmokers who did not use COCs [4].Since the VTE risk is greatest in the first few months of use, and then falls, (Figure 1), when comparing VTE risks of different COCs, it is important to account for the recency of intitiation, and ensure that new users of one pill are being compared to new users of the other pill. Indeed, the VTE risk is transiently higher even in women who restart COC use after a break [5,6].

Following the publicity about VTE risk and the COC, the European regulatory authority (EMA) requested a large postmarketing surveillance study. This study, the European Active Surveillance study on Oral Contraceptives (EURAS), enrolled over 58,000 women, with results for 142, 475 woman-years, and suggests no difference in VTE rates between second- and third-generation oral contraceptive pills, or Yasmin® [7]. The scale of the study, amount of detailed prospective information collected about each woman (with regard to relevant cardiovascular risk factors), validation of all VTE diagnoses by review of medical records and the fact that only 2.4% of women were lost to follow-up, make this an important investigation.

Keywords: BMI • contraception • drospirenone • levonorgestrel • venous thromboembolism • VTE

10.1586/EOG.11.52

ISSN 1747-4108

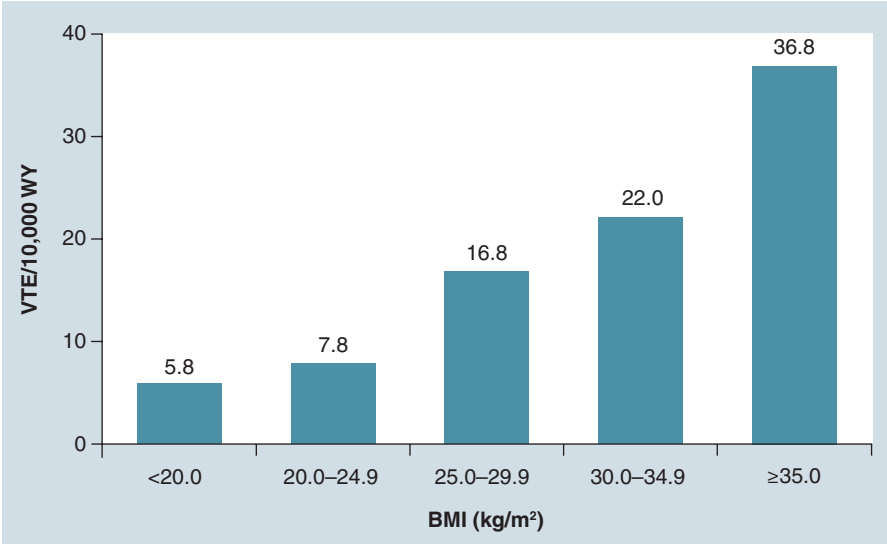

Figure 1. Risk of venous thromboembolism by body mass index.
VTE: Venous thromboembolism; WY: Woman-years.
Reproduced with permission from [5].

The EURAS study also suggests all VTE rates are higher than previously thought: approximately 90 per 100,000 woman-years for the COC, and on average 290 per 100,000 woman-years in pregnancy. For women with a BMI over 30 kg/m^2, the risk was 230 per 100,000 woman-years. Increasing age was also a significant risk factor. As has been noted in previous studies of cardiovascular risks, women using the newest COC preparation (in this case Yasmin) were at higher risk at entry, presumably as a result of prescriber bias (in particular they were more likely to be obese (Figure 2)). Non-pregnant, nonusers in a comparable population sample had a VTE risk of 44 per 100,000 woman-years [8].

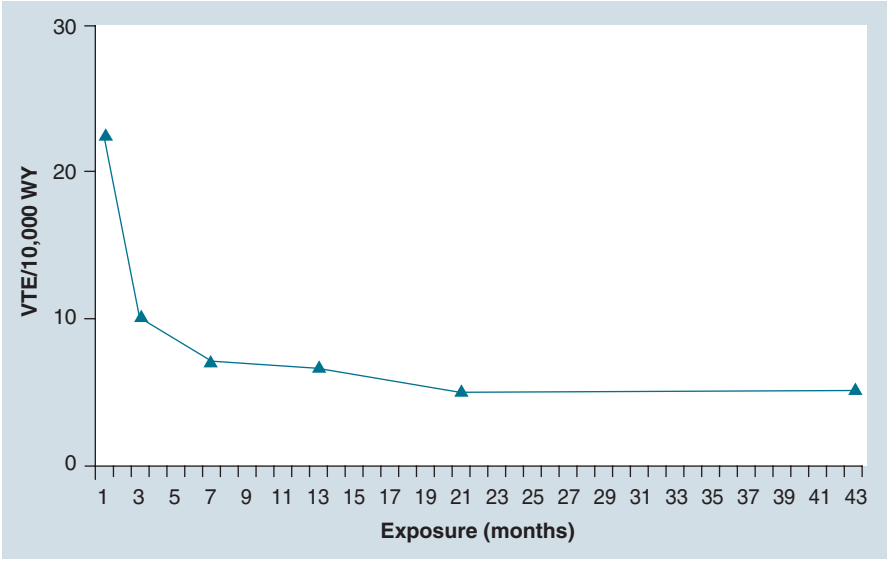

Figure 2. Venous thromboembolism risk over time following start of combined oral contraceptive use.
VTE: Venous thromboembolism; WY: Woman-years.
Reproduced with permission from [5].

Other well-controlled studies since 1995 have come to similar conclusions with regard to VTE risk, both in the USA [9] and Germany [10].

In 2009, two studies were published, again suggesting that risks of VTE were increased with newer pills, However, they failed to take confounding factors such as obesity, family history, duration of use and preferential prescribing (of newer pills to higher-risk women) into account [2,6]. In its assessment of both studies, the US FDA concluded that, because of the methodological flaws, their results were unreliable [6].

In April 2011, the Boston Collaborative Drug Surveillance Program group published two case–control database studies, one from the USA and one from the UK [5]. These purported to show an increased risk of VTE in users of drospirenone (DRSP)-containing COCs compared with levonorgestrel-containing COCs. Yet again, there was lack of validation of VTE cases and lack of information on, or control of, important potential confounders such as full allowance for duration of use (especially short-duration use), family history, BMI; and smoking. Most cases of VTE are associated with few symptoms, and a swollen leg may turn out not to be a deep vein thrombosis (DVT) on further investigation. However, because of the known association between use of COCs and VTE, and in particular as a result of all the publicity surrounding the newer COCs and VTE risk, women using such pills are more likely to be sent for investigation than those who do not. If the diagnosis is not then validated (i.e., confirmed), but simply based on the presumed diagnosis on admission, diagnostic bias results [5].

These studies, as have database studies before them, under-ascertained the incidence of VTE, which increases the likelihood of diagnostic and treatment bias among DRSP users. It is likely that this is due, in part, to their decision to only include what they considered to be 'idiopathic' cases (i.e., where there appeared to be no known risk factors). However, VTE is a multicausal condition and many of the risk factors are common in the general population: genetic factors such as Factor V Leiden and other clotting disorders combine over a period of time with acquired risk factors, such as pregnancy, puerperium, use of COCs, increasing age, obesity and immobilization. Thus, a combination of risk factors in one person is common and risk factors may not always be obvious (e.g., 'new' clotting disorders are regularly being

diagnosed; we should not forget that Factor V Leiden was only recognised in 1994) [11,12]. Such restriction therefore fails to account for unmeasured confounders and biases and leads to analyses that are not representative of the population risk of VTE [5,13].

In the UK GP Research Database study there were very few cases and controls in the DRSP group [14]; in many areas of the UK there are prescribing restrictions on the use of DRSP COCs, because of their higher price; this must result in a selective tendency for women at high risk of VTE to use these pills [13]. The authors asserted that there is no clear evidence for any noncontraceptive benefits of DRSP-containing COCs; however, such pills have been granted a licence in the USA for both treatment of acne and severe premenstrual syndrome, on the basis of their efficacy [15].

A reanalysis of the Danish Cohort Study originally published in 2009 [16] has been requested by the Medicines Evaluation Board on behalf of the Pharmacovigilance Working Party of the EMA. The reanalysis requested is to focus on the time period between 2001 and 2005, reflecting the initial introduction of DRSP COCs in the Danish market, in an effort to avoid the effect of 'left truncation' by comparing similar durations of current COC use (one of the major problems with this study was that many levonorgestrel-containing COC users were classified as short-term, instead of long-term users, since the study began in 1995, while DRSP-containing COCs did not appear on the market until 2001). However, that analysis still cannot adjust for the confounders of BMI, family history and smoking, since this information is not collected by the registry. In addition, a recent publication from Denmark suggests that the incidence of VTE could not reliably be assessed in the Danish registry [17]. Thus, it is difficult to see how much useful information the reanalysis will actually provide.

What lessons have we learned since 1995? Many epidemiologists appear to have learned very little, but clinicians need to weigh up risks and benefits for individual patients. The UK Committee on Safety of Medicines has twice issued statements suggesting that COCs (regardless of type) should be prescribed with caution to women whose BMI is over 30, first in 2004 and most recently in May 2011 following publication of the *BMJ* papers [101]. 15 years ago, there were relatively few alternatives to the combined pill. However, as highly effective progestogen-only contraceptives, which do not increase VTE, are now available, the prescribing of COCs to women with a BMI >30 kg/m^2, and particularly those with multiple risk factors for cardiovascular disease, is becoming difficult to justify [1].

Financial & competing interests disclosure

The author has received conference sponsorship, consultancy fees and lecture fees from Wyeth, Organon (now Merck Sharpe & Dohme) and Schering (now Bayer-Schering). The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
•• of considerable interest

1 Szarewski A, Mansour D, Shulman L. 50 years of 'The Pill': celebrating a golden anniversary *J. Fam. Plann. Reprod. Health Care* 36(4), 231–238 (2010).

2 Shapiro S, Dinger J. Risk of venous thromboembolism among users of oral contraceptives. A review of two recently published studies. *J. Fam. Plann. Reprod. Health Care* 36(1), 33–38 (2010).

3 Pomp ER, le Cessie S, Rosendaal FR, Doggen CJ. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. *Br. J. Haematol.* 139, 289–296 (2007).

4 Pomp ER, Rosendaal FR, Doggen CJ. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. *Am. J. Hematol.* 83, 97–102 (2008).

5 Heinemann K, Heinemann LAJ. Comparative risks of venous thromboembolism among users of oral contraceptives containing drospirenone and levonorgestrel. *J. Fam. Plann. Reprod. Health Care* 37, 132–135 (2011).

•• **Comprehensive critique of the 2011 venous thromboembolism (VTE) papers from the Boston group.**

6 Reid RL, Westhoff C, Mansour D *et al.* Oral contraceptives and venous thromboembolism consensus opinion from an international workshop held in Berlin, Germany in December 2009. *J. Fam. Plann. Reprod. Health Care* 36(3), 117–122 (2010).

•• **Review of the issue of VTE and the combined oral contraceptive (COC) by an international group of experts.**

7 Dinger JC, Heinemann LA, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. *Contraception* 75(5), 344–354 (2007).

•• **The most reliable study thus far on risks of VTE with COCs.**

8 Heinemann LA, Dinger JC. Range of published estimates of venous thromboembolism incidence in young women *Contraception* 75, 328–336 (2007).

9 Seeger JD, Williams PL, Walker AM. An application of propensity score matching using claims data. *Pharmacoepidemiol. Drug Safety* 14(7), 465–476 (2005).

10 Dinger J, Assmann A, Mohner S, Minh TD. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case–control study. *J. Fam. Plann. Reprod. Health Care* 36(3), 123–129 (2010).

11 Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 353, 1167–1173 (1999).

•• **Excellent and clear explanation of VTE mechanisms.**

12 Chan KT, Tye GA, Popat RA *et al.* Common iliac vein stenosis: a risk factor for oral contraceptive-induced deep vein thrombosis. *Am. J. Obstet. Gynecol.* DOI: 10.1016/j.ajog.2011.06.100 (2011) (Epub ahead of print).

13 Szarewski A, Mansour D. The pill and thrombosis: study subject to unmeasured confounders and biases *BMJ* 342, d3349 (2011).

14 Parkin L, Sharples K, Hernandez RK, Jick S. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *BMJ* 342, d2139 (2011).

15 Panay N. Management of premenstrual syndrome. *J. Fam. Plann. Reprod. Health Care* 35(3), 187–194 (2009).

16 Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 339, b2890 (2009).

17 Severinsen MT, Kristensen SR, Overvad K, Dethlefsen C, Tjønneland A, Johnsen SP. Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. *J. Clin. Epidemiol.* 63, 223–228 (2010).

Website

101 MHRA: Drug Safety Update, 4(11), A2 (2011) www.mhra.gov.uk/home/groups/dsu/documents/publication/con120237.pdf