Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study

Jürgen Dinger, Anita Assmann, Sabine Möhner, Thai Do Minh

Abstract
Objective The primary objective of the study was to clarify whether the use of the oral contraceptive 2 mg dienogest/30 µg ethinylestradiol (DNG/EE) is associated with a higher risk of venous thromboembolism (VTE) than the use of other combined oral low-dose contraceptives (i.e. containing ≤30 µg EE), particularly oral contraceptives containing levonorgestrel (LNG). The secondary objective was to investigate the VTE risk associated with drospirenone/ethinylestradiol (DRSP/EE) in comparison to low-dose LNG/EE.

Methods This German community-based, case-control study recruited VTE cases from the primary care sector. Eligible cases were women aged 15–49 years with a VTE between January 2002 and February 2008. Four controls (women without a confirmed or potential VTE before the index date) were matched by age and region to each case. Medical information relevant for the assessment of VTE was abstracted from patient charts. Data on personal characteristics of the patients were collected via self-administered questionnaires. At the end of the study a blinded adjudication of the reported VTE was conducted. Conditional logistic regression techniques were used, adjusting for nine potential confounders, including personal history of VTE, family history of VTE, body mass index, duration of current combined oral contraceptive (COC) use and smoking.

Introduction
The association between combined oral contraceptive (COC) use and venous thromboembolism (VTE), which is generally attributed to the estrogen dose, has been known since these products were first introduced in the 1960s. Consequently, the dose of estrogen in oral contraceptives (OCs) has been reduced substantially, with a concomitant decrease in the associated risk of thromboembolic events.

More recently, scientific discussion of the VTE risk associated with COC use has focused on the type of progestogen. Since 1995, several epidemiological studies have suggested an increased risk of VTE with COCs containing desogestrel, or gestodene as the progestogen component (so-called ‘third-generation’ progestogens), compared with COCs containing levonorgestrel (LNG) and other so-called ‘second-generation’ progestogens, which contained the same dose of estrogen.1–4 However, studies utilising improved methodology to control for bias and confounding were unable to confirm these original risk estimates,5–10 leading to suggestions that the differential risk was overestimated due to bias and confounding factors.11

This issue has been revisited by two studies recently published in the same issue of the British Medical Journal, a retrospective cohort study in Denmark12 and a case-control study in The Netherlands.13 They found that relative to LNG-containing COCs, desogestrel- and gestodene-containing COCs do indeed carry a higher risk of VTE. In addition, the authors suggested that COCs containing drospirenone (DRSP) might also carry a higher risk. Dienogest (DNG) was not investigated in these studies. The methodological limitations of these studies are discussed elsewhere.14,15

The finding regarding DRSP is not consistent with findings from two large prospective cohort studies specifically designed to evaluate the risk of VTE among women using DRSP. In a study of almost 60 000 European women there was no evidence of an increased risk of VTE among users of DRSP relative to users of LNG.16 That study excluded long-term users and full provision was

Results A total of 680 VTE cases and 2720 corresponding controls were analysed. The mean age of cases and controls was – as a result of matching – almost identical (36.1 years). A total of 35, 25, and 60 of the cases had used DNG-, DRSP- and LNG-containing low-dose COCs, respectively, at the time of the VTE diagnosis. The crude odds ratio (OR) for VTE associated with current COC use in comparison to women who had never used a COC before the index date was 1.9 (95% CI 1.5–2.5), the adjusted OR was 2.3 (95% CI 1.7–3.0). The point estimate of the crude OR of DNG/EE vs any other low-dose COCs was 0.9 (95% CI 0.6–1.3), the adjusted OR was 0.9 (95% CI 0.6–1.4). The crude ORs for DNG/EE and DRSP/EE vs low-dose LNG/EE were 1.1 (95% CI 0.7–1.8) and 1.0 (95% CI 0.6–1.6), respectively; the adjusted ORs were 1.1 (95% CI 0.7–1.9) and 1.0 (95% CI 0.6–1.8).

Conclusions The study confirms that COC use is associated with an increased risk of VTE. The VTE ORs (adjusted and crude) that compared DNG/EE and DRSP/EE with other low-dose COCs (including LNG/EE) were close to unity and do not indicate a higher risk for users of DNG/EE or DRSP/EE.

Keywords case-control study, dienogest, drospirenone, oral contraceptives, venous thromboembolism

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Key message points
- The study confirms that use of combined oral contraceptives (COCs) is associated with an increased risk of venous thromboembolism (VTE).
- The risk of VTE for users of COCs containing dienogest or drospirenone is similar to that for users of COCs containing other progestogens.
made in its design and analysis to control for confounding by multiple factors, including duration of current COC use, obesity and family history of VTE. Also, in the other large cohort study of almost 67,000 women carried out using an automated claims database in the USA, no evidence of an increased risk of VTE was found among DRSP users relative to users of COCs containing other progestogens, including LNG.17

Overall, there are two prevailing interpretations of existing data on COC use, progestogens and the risk of VTE. One claims that specific progestogens have a differential impact on the risk of VTE whilst the other concludes that (1) the risk of VTE attributable to COCs is a class effect primarily dependent on the estrogen dose and (2) the overall as well as the differential impact of progestogens is small.

Regardless of the interpretation used, the purpose of the present study is to provide an additional set of empirical data to enable clearer conclusions to be drawn. In so doing, and drawing on increasing discussion of factors that could impact rates of VTE in users of COCs, the following potential types of confounding and bias are of relevance.

(1) One factor that needs to be accounted for when examining the differential risk of VTE in populations of OC users is the current duration of COC use. Data show that the length of time a COC has been taken affects the risk of VTE such that this risk is highest during the first 6 to 12 months (and particularly during the first 3 months), declines thereafter and eventually becomes stable at a lower level.16 Studies that have adjusted for duration of use have found lower risk estimates for the ‘third-generation’ progestogens desogestrel and gestodene than those that have not.

(2) Related to current duration of use is the factor known as ‘attrition of susceptibles’.2,4,18,19 This describes the tendency that adverse drug reactions occur in those members of a given COC user population who are susceptible to certain side effects (due to the presence of inherited, acquired and/or behavioural risk factors such as family history of VTE, factor V Leiden mutation, frequent long-haul flights or obesity) at an early stage, which leaves the original population with fewer ‘susceptibles’. In other words, a marked drop is seen in a user population’s percentage of susceptible members relatively soon after a new preparation is introduced, which then flattens out with continued use. As such, it can be misleading to compare a user population for a newly introduced product with one for a product that has been on the market for a longer period of time due to a substantially higher percentage of short-term susceptible members in the former. Specifically, it has been suggested that the potentially heightened risk of VTE in women taking so-called ‘third-generation’ COCs may be derived in part from bias based on attrition of susceptibles.19

(3) An increased risk of VTE with newer versus older preparations may also occur because of preferential prescribing of newer products to women with risk factors such as obesity or family history of VTE, which would be instances of confounding by indication. It has been argued18,20–23 that so-called ‘third-generation’ COCs were preferentially prescribed to women at risk of a COC-associated adverse event because of their perceived improved safety profile.

(4) Higher VTE rates with so-called ‘third-generation’ versus ‘second-generation’ oral contraceptives may also have been the result of referral (diagnostic) bias. Evidence shows24 that women with symptoms of VTE who used COCs were more often referred for further diagnosis at specialised centres than women who were not using COCs. In addition, women with risk factors for VTE (who disproportionately received ‘third-generation’ COCs) may have been more often referred to specialist centres than users of ‘second-generation’ COCs.

In 1995, a monophasic, low-dose COC containing 2 mg DNG and 30 µg ethinylestradiol (EE) (DNG/EE) was introduced to the German market. In addition to its contraceptive effectiveness, DNG possesses anti-androgenic properties and is therefore used to treat androgen-related conditions such as acne and polycystic ovarian syndrome.3–5 A monophasic, low-dose combination of 3 mg DRSP and 30 µg EE (DRSP/EE) was introduced to the German market in late 2000. DRSP is a progestogen with anti-androgenic as well as antiminalocorticoid activity. 25

For the past decade, the COC containing DNG/EE has been the most widely used OC brand in Germany. Although DNG/EE is generally well tolerated,26–28 to date there are no sufficiently powered studies investigating the risk of VTE with this preparation. The present study was carried out to assess the risk of VTE in users of DNG/EE and, separately, DRSP-containing COCs, relative to other low-dose COCs, particularly those containing LNG. The study was conducted more than a decade after the introduction of DNG/EE to the market, which minimises the influence of bias related to attrition of susceptibles (differential duration of use). Due to its later market introduction this does not apply to the same extent to DRSP/EE. However, many of the above mentioned methodological considerations on the reduction of bias and residual confounding (such as reduction of referral and selection bias by conducting the study as a community-based field study) had the potential to improve the validity of the results on DNG/EE as well as DRSP/EE.

Methods

Study design

This was a community-based, case-control study conducted in Germany between June 2007 and May 2008. The study centres included outpatient offices from the primary care sector as well as specialised diagnostic centres from all federal states of Germany. The study protocol, questionnaires, and informed consent forms were designed to comply with German law and were approved by the Ethics Committee of the Berlin Medical Association. The study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices,29 Good Epidemiological Practice30 and the ethical principles of the Declaration of Helsinki. All women provided written informed consent prior to entry into the study. Women without informed consent and/or who were unable to communicate in German were excluded from the study.

Study population

Cases

A randomly selected sample of 250 primary care physicians, internists, gynaecologists and radiologists from all federal states of Germany were contacted by mail regarding whether they had seen any cases of VTE between January 2002 and February 2008. Eligible cases were women, aged 15–49 years, with a clinical diagnosis of VTE. The diagnosis of VTE [deep vein thrombosis (DVT) or pulmonary embolism] had to be confirmed by imaging procedures or clinical examination plus a positive result from a less specific diagnostic test and/or specific anticoagulatory treatment. Eligible cases were asked by their physicians to participate in the study, and completed a questionnaire on personal characteristics, symptoms and signs of VTE, and potential risk factors for VTE. The
questionnaire was designed to collect data on age, past and current use of hormonal contraception, body weight and height, smoking habits, personal and family history of VTE, varicose veins, recent immobilisation, pregnancy, surgery and accidents, and genetic risk factors as well as chronic diseases, concomitant medication, socioeconomic and lifestyle indicators. In addition, the medical records for all eligible cases were abstracted by the reporting physician using a questionnaire, focusing on results of diagnostic procedures and therapeutic measures. Missing or illegible information was requested from the study cases or physicians by telephone interviews.

All reported cases of VTE were classified as one of the following: (i) definite VTE (i.e. confirmed by imaging procedures with high specificity such as phlebography, Duplex sonography or magnetic resonance imaging (MRI) for DVT, or spiral computed tomography or angiography for pulmonary embolism); (ii) probable VTE (i.e. clinical diagnosis confirmed by a physician and supported by an unspecific diagnostic test such as D-dimer and/or a subsequent specific therapy such as fibrinolysis or long-term anticoagulatory therapy); or (iii) no VTE (i.e. validation that does not yield the final diagnosis ‘VTE’). To avoid inconsistent and/or biased classification of VTE, a blinded adjudication committee comprising three physicians (specialised in internal medicine and clinical pharmacology) used pre-specified criteria to identify all reported VTEs. The procedure consisted of: (a) independent adjudication by the specialists; (b) documentation of the individual assessments; (c) comparison of the individual assessments; (d) discussions of ‘split decisions’; (e) re-adjudication of the discussed cases; and (f) documentation of the individual assessments after re-adjudication. For the purpose of this study, a conservative approach was taken and a reported VTE was classified as definite if at least one of the adjudicators (before the discussion of ‘split decisions’) classified it as confirmed.

Controls
Each VTE case was matched with four community-based controls [i.e. women without confirmed or potential VTE between January 2002 and the event date of their matched case (i.e. index date)] according to year of birth and area of residence. The controls were identified from randomly selected households within the same town as the respective case using a strict statistical procedure (random route procedure) that gave all women in the relevant area the same chance of selection. These neighbourhood controls were contacted at their homes by trained interviewers, and asked to complete a similar questionnaire (without case-specific questions regarding VTEs) as for the cases. The same exclusion criteria for the cases were applied to the selection of controls.

Statistical analysis
The sample size calculation was based on a two-sided α of 0.05, a power of 0.90 and the estimated prevalence of DNG/EE use among women of fertile age. Market research suggested that 13% of German OC users were users of DNG/EE. Assuming that at least 30% of German women of fertile age are current users of OCs, a prevalence of current use of DNG/EE of about 4% was estimated. Based on these data, approximately 500–700 cases and 2000–2800 controls would be needed to exclude a two-fold increased risk of VTE compared to LNG/EE. DRSP/EE was also widely used since the early 2000s, and the statistical power to exclude a two-fold increased risk of VTE was approximately 80%.

The analysis of this case-control study was performed with the statistical package SAS® 9.1 software (SAS Institute Inc., Cary, NC, USA) using conditional logistic regression models. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the following comparisons: DNG 2 mg/EE 30 µg vs low-dose LNG-containing COCs, DRSP 3 mg/EE 30 µg vs low-dose LNG-containing COCs and DNG 2 mg/EE 30 µg vs other low-dose COCs (≤30 µg EE). The conditional logistic regression model included nine potential confounders: personal history of VTE, family history of VTE, body mass index (BMI), duration of current COC use, parity, educational level, chronic disease, concomitant medication and smoking.

The primary objective of the study was to clarify whether the use of DNG/EE is associated with a higher risk of VTE than the use of low-dose LNG-containing COCs. The primary analysis was based on the comparison of the upper confidence limit for the point estimate of the VTE OR with the predefined non-inferiority limit of 2. The null hypothesis was VTE OR ≥2 (i.e. the VTE OR for DNG/EE vs low-dose LNG-containing COCs is higher than or equal to 2). The alternative hypothesis was: VTE OR<2.
Table 1 Blinded adjudication: number of unanimous and split decisions for confirmed and unconfirmed cases, respectively, of venous thromboembolism

<table>
<thead>
<tr>
<th>Decision</th>
<th>Confirmed cases* (n)</th>
<th>Unconfirmed cases (n)</th>
<th>Total cases (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanimous decision</td>
<td>674</td>
<td>0</td>
<td>674</td>
</tr>
<tr>
<td>Split decision</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>681</td>
<td>0</td>
<td>681</td>
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</table>

*One patient withdrew her informed consent after adjudication, therefore the analysis is based on 680 cases.

Table 2 Comparison of population characteristics of cases and controls in the present study

<table>
<thead>
<tr>
<th>Population characteristic</th>
<th>Cases (n = 680)</th>
<th>Controls (n = 2720)</th>
<th>Total (n = 3400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>680</td>
<td>2720</td>
<td>3400</td>
</tr>
<tr>
<td>Mean age [years, (SD)]</td>
<td>36.1 (9.0)</td>
<td>36.1 (9.0)</td>
<td>36.1 (9.0)</td>
</tr>
<tr>
<td>Body mass index ≥30 kg/m² [n, (%)]</td>
<td>144 (21.2)</td>
<td>362 (13.3)</td>
<td>506 (15.0)</td>
</tr>
<tr>
<td>Ever use of hormonal contraceptives [n, (%)]</td>
<td>756 (84.7)</td>
<td>2197 (80.8)</td>
<td>2953 (87.0)</td>
</tr>
<tr>
<td>Current oral contraceptive use [n, (%)]</td>
<td>273 (40.1)</td>
<td>814 (29.9)</td>
<td>1087 (31.0)</td>
</tr>
<tr>
<td>Family history of VTE [n, (%)]</td>
<td>208 (30.6)</td>
<td>350 (12.9)</td>
<td>558 (16.5)</td>
</tr>
<tr>
<td>Personal history of VTE [n, (%)]</td>
<td>50 (7.4)</td>
<td>57 (2.1)</td>
<td>107 (3.2)</td>
</tr>
</tbody>
</table>

SD, standard deviation; VTE, venous thromboembolism.

The study’s secondary objective was to examine whether the use of DRSP/EE is associated with a higher risk of VTE than low-dose LNG-containing COCs.

Results

Overall, 179 out of 250 (71.6%) contacted physicians participated in the study; of these, 105 (59%) were general practitioners, 48 (27%) internists, 25 (14%) gynaecologists, and one was a radiologist (1%). A total of 879 women with a VTE during the study period (cases) and 4323 controls were asked to participate in the study; 115 cases (13.1%) and 412 controls (9.5%) refused to participate or did not respond. The flow of cases and controls throughout the study, including reasons for discontinuation, are presented in Figure 1(a) and Figure 1(b), respectively.

Independently of each other, the blinded adjudicators assigned a total of 674 reported events to the ‘confirmed VTE’ category. For seven events the adjudicators arrived at a ‘split decision’ (Table 1). According to the conservative approach defined in the study protocol (see Methods section), split and unanimous decisions result in a total of 681 confirmed VTE cases. After the adjudication process one patient withdrew her informed consent. Therefore, the inferential statistics were based on 680 cases and 2720 controls.

A summary of the general characteristics of the cases and controls is provided in Table 2. Current and ever-use of COCs, obesity, family and personal history of VTE were more prevalent among the cases compared to the controls.

The number of women who were never, ever, current or past COC users at index date is shown in Table 3. Tables 4 and 5 show the number of women exposed to the COCs of interest at index date.

Current COC use was associated with about a two-fold increased risk of VTE compared with no use (Table 6a). Adjustments for nine potential confounders increased the risk estimate for current COC users. Use of DNG/EE was associated with a similar VTE risk compared with use of other low-dose COCs, including low-dose COCs containing LNG (Table 6b and 6c). Adjustment for potential confounders resulted in slight or no changes in the risk estimates. In the analysis for DRSP/EE (Table 6d), the results were similar to those for DNG/EE, thus allowing similar conclusions regarding VTE risk to be made for DRSP/EE. The upper 95% CIs for the adjusted ORs for the other low-dose COCs, including low-dose COCs containing LNG were below 2 (Figure 2).

A sub-analysis of idiopathic VTE (events not associated with acute risk factors for VTE such as pregnancy, trauma, immobilisation, surgery, cancer and chemotherapy)
resulted in crude ORs for DNG/EE and DRSP/EE vs low-dose LNG/EE of 1.0 (95% CI 0.6–2.0) and 0.7 (95% CI 0.3–1.4), respectively. The adjusted ORs were 1.1 (95% CI 0.5–2.1) and 0.6 (0.3–1.5).

Discussion
The present study confirms that current COC use is associated with an increased risk of VTE compared with never use. The risk estimates for DNG/EE do not suggest that it is associated with a higher risk of VTE than other low-dose COCs or low-dose LNG/EE. With the given statistical power of this study, a two-fold increased risk of VTE in users of DNG/EE compared with other low-dose COCs or with low-dose LNG/EE can be excluded. These findings are consistent with that of a previous case-control, community-based study conducted in Germany showing no indication of a higher VTE risk in users of DNG/EE compared with users of so-called ‘first-’ and ‘second-generation’ progestogens (i.e. a progestogen component other than DNG, gestodene, desogestrel or DRSP).34

In addition, the present study suggests that DRSP/EE is not associated with a higher risk of VTE relative to low-dose LNG/EE. This observation is consistent with two previous prospective, comparative, cohort studies with approximately 60 000 and 67 000 study participants, respectively, including a total of more than 42 000 woman-years of exposure to DRSP/EE, which failed to find any evidence of increased VTE risk among users of other COCs (and LNG/EE).16,17 In contrast, a recent case-control study conducted in The Netherlands13 and a retrospective cohort study in Denmark12 suggested an elevated VTE risk for DRSP/EE relative to LNG/EE. In the Dutch case-control study, the accrual of cases from highly specialised centres as well as the selection of controls and the non-use of potential confounders in the statistical model are methodologically questionable. Furthermore, the results were not statistically significant. In the Danish cohort study, selective misclassification of short-term use, non-availability of potential confounders and misclassification of VTE make it difficult to differentiate between bias, residual confounding and causation.15 Overall, the results of the present study support the results of the two prospective cohort studies that did not show an increased risk of VTE for DRSP/EE relative to LNG/EE.

This also applies to the risk estimates for ‘idiopathic VTE’, although conceptually their interpretation is difficult. VTEs are not mono-causal. Classification of a VTE as ‘idiopathic’ reflects only the current scientific knowledge and will change over time. The assessment of VTE is difficult, and excluding VTE cases with known causes makes it even more difficult. This would be analogous to excluding those patients who have diabetes in addition to acute myocardial infarction from the primary analysis of atherosclerotic arterial disease. In addition, there is considerable potential for misclassification bias.

Table 6 Crude and adjusted odds ratios for venous thromboembolism cases among users of dienogest/ethinylestradiol and drospirenone/ethinylestradiol in comparison to any other low-dose combined oral contraceptive, and low-dose levonorgestrel/ethinylestradiol

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Point estimate</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>(a) COC use vs no use</td>
<td>ORcrude 1.9</td>
<td>1.5–2.5</td>
</tr>
<tr>
<td></td>
<td>ORadj9 2.4</td>
<td>1.8–3.2</td>
</tr>
<tr>
<td>(b) DNG/EE vs other low-dose COCs</td>
<td>ORcrude 0.9</td>
<td>0.6–1.6</td>
</tr>
<tr>
<td></td>
<td>ORadj9 0.9</td>
<td>0.6–1.4</td>
</tr>
<tr>
<td>(c) DNG/EE vs low-dose LNG/EE</td>
<td>ORcrude 1.1</td>
<td>0.7–1.8</td>
</tr>
<tr>
<td></td>
<td>ORadj9 1.0</td>
<td>0.6–1.8</td>
</tr>
<tr>
<td>(d) DRSP/EE vs low-dose LNG/EE</td>
<td>ORcrude 1.0</td>
<td>0.6–1.6</td>
</tr>
<tr>
<td></td>
<td>ORadj9 1.0</td>
<td>0.5–1.8</td>
</tr>
</tbody>
</table>

adj9, Adjusted for personal history of venous thromboembolism (VTE), family history of VTE, body mass index, duration of combined oral contraceptive use, parity, educational level, chronic disease, concomitant medication and smoking; CI, confidence interval; COC, combined oral contraceptive; DNG, dienogest; DRSP, drospirenone; EE, ethinylestradiol; LNG, levonorgestrel; OR, odds ratio.
because the search for causes is most likely stopped after the first reason is identified. In this case it is conceivable that attending physicians would stop searching after identifying COC use as a ‘risk factor’. Also, it is not possible to arrive at a quantification of the absolute risk under ‘real life conditions’.

In observational research the possibility of bias and residual confounding can never be entirely eliminated, and the ability to infer causation or to exclude substance-specific risk is correspondingly limited.25 Although known potential confounders were documented at baseline, adjustment cannot be done for unknown confounders. The risk estimates calculated in the present study should therefore be interpreted with care, and the relatively low 95% upper confidence limit for the OR for ‘idiopathic VTE’ with DRSP/EE vs low-dose LNG/EE, for example, should only be interpreted such that a two-fold risk can be excluded.

The impact of selection bias is probably low as cases and controls were selected from the primary care sector and the neighbourhood of the cases, respectively. Nevertheless, it has to be acknowledged that some of the contacted physicians, cases and controls refused to participate. Although the refusal rates were relatively small in comparison to other studies this might have biased the study results. A second potential source of bias in this retrospective case-control study is that we could recruit only survivors of VTE. However, given that the fatality rate associated with VTE is lower in women of fertile age is about 1%,36 this cannot have a substantial effect on the risk estimates.

Other types of bias that played a role in several other studies on VTE were probably only of minor importance in the present study. For example, our study was performed more than a decade after the launch of DNG/EE in Germany and therefore attrition of susceptibles should not be much of an issue. This does not apply to DRSP/EE. In any event, the effect in this case would result in erroneously high risk estimates for DRSP/EE and would therefore not lead to underestimating a safety issue.

Moreover, our study was able to make use of information on personal/family history of VTE and BMI. These risk factors for VTE are probably the most important potential confounders to account for the specific risk associated with the DNG/EE and DRSP/EE user populations.

The possibility exists that diagnostic bias may have influenced the odds ratio for COC use compared to non-use. Clinical symptoms of VTE cover the spectrum from a complete absence of symptoms or unspecified, slight ones37 to dramatic, acute, life-threatening symptoms. Therefore it is to be expected that the frequency of diagnostic procedures to clarify unspecific and mild to moderate symptoms – increases with the physician’s and patient’s awareness of a COC-related VTE risk (leading to a potential overestimation of the risk in COC users). However, during the study period the VTE risk associated with DNG/EE and DRSP/EE was not widely discussed in Germany. Therefore, it is unlikely that the risk estimates for the direct comparison of DNG/EE, DRSP/EE and low-dose LNG/EE were differentially biased. Even more important, referral bias – a subtype of diagnostic bias – did not play a role in this study, as this community-based study was not focused on specialist diagnostic centres for VTE.

In contrast, many of the previous case-control studies investigating the risk of VTE associated with ‘second-’ and ‘third-generation’ COCs identified cases via specialised centres/hospitals, and were therefore likely to have been affected by referral bias (i.e. primary care physicians may have preferentially referred COC users with symptoms potentially indicative of VTE to specialised diagnostic centres compared with non-OC users who had non-specific, mild VTE symptoms).19,38

Whilst recall bias is a problem in all studies dealing with information from the past, there is no reason to assume a relevant differential effect for the exposures of interest. Since data capture and validation of VTE outcomes were highly standardised, the chance of reporting-related differences between these exposures is low. In fact, it is conceivable that VTE cases were better motivated to identify COC exposure (as a potential cause of VTE) compared to controls (again leading to an overestimation of the VTE risk associated with COC use in general).

In conclusion, the present case-control study suggests that the risk of VTE in users of DNG/EE OCs is similar to the risks associated with the use of low-dose LNG/EE and other low-dose COCs. Additionally, this study did not find any evidence of increased VTE risk among users of DRSP/EE compared with users of low-dose LNG/EE.

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Competing interests None identified.

References


Eventually, the arranged marriage is completed and Nina moves to join her husband in Canada. She is isolated and unsure; her Indian culture has taken away access to Andy’s friends and relations. She buys Western clothes that make her look plump and middle-aged. Andy thinks she needs nothing but him and will soon be a mother.

Andy dwells on his premature ejaculation; Nina, bored and lonely (she cannot teach without re-qualifying), finds her way to the library where she devours the books and tries to make Andy read about sexual therapy. Andy secretly goes off to have surrogate sexual therapy, which sounds very provocative to Andy’s behavior more than he does. The storyline drifts along and the occasional sentence construction and proofreading errors are irritating. The contrasts between the propriety of too many people, the overwhelming impressions of Indian culture, and the cool, solitary, and often isolated life in Canada are striking. The certainties of the codes of conduct and obligations to relations in India are contrasted with the ambiguous confusing lack of accountability in Canada, adding to our understanding of the different cultures. Much of the book is about the adjustments, difficulties and misunderstandings in marriage. Couples may marry for love, for money because of pregnancy, convenience, or by arrangement. The differences between the necessary adjustments between two people in this arranged marriage and any other seem slight, except that these two people are isolated from their traditional ways of behaving and have to find, or perhaps are enabled to find, their own solutions.

Reviewed by Gill Wakley, MD, FFSRH
Retired Professor of Primary Care Development and Freelance Writer, Abergavenny, UK


Nina, a lecturer in English at a college in Delhi, dreads her thirtieth birthday. She is still unmarried, a condition much bewailed by her mother. Following her diplomat father’s death, she and her mother had been forced to live in reduced circumstances, first with her disapproving grandparents and now sharing one room. Their every move is noticed and commented on by others.

Her mother arranges an astrologer reading and from this follows an introduction to the family of Annika who is seeking a bride. Annika is in Canada working as a dentist having re-qualified there. He left India after his parents were killed in an accident, initially to join his uncle who is married to a Canadian. Annika has survived the first intense loneliness and the confusion of circumstances, first with her disapproving mother, then arranged marriage and any other seem slight, except that these two people are isolated from their traditional ways of behaving and have to find, or perhaps are enabled to find, their own solutions.

We hope that journal readers enjoyed reading The Immigrant, and also discovering whether their opinion of this book matched that of our guest reviewer. In the October 2010 issue, the fiction book section will be Private Life by Jane Smiley (318 pages, Faber & Faber, 2010, ISBN-13: 978-0-571-25874-1, £12.99, paperback). We also hope to review two other books that Journal readers might be interested in reading: Antigona and Me by Katie Clanchy (273 pages, Picador, ISBN-13: 978-0-230-76006-8, paperback of an Outcast Season and Daughters of Dust: Growing Up in an Outsider Family, 1996) and Up An Outcast Sky by Michael Morpurgo (312 pages, ISBN-13: 978-1847396358, £7.99, paperback). We want to remind journal readers that if they would like to offer to review an appropriate fiction title of their own choice then they should contact the Journal Editorial Office by e-mail (journal@fsrh.org) in the first instance with details of their nominated title.
Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study

Jürgen Dinger, Anita Assmann, Sabine Möhner and Thai Do Minh

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