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Safety of a New Oral Contraceptive Containing Drospirenone

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Abstract

New chemical entities must undergo rigorous, and preferably independent, safety and efficacy assessments before entry into the market. This is also true for oral contraceptives (OCs) given their extensive usage by healthy women and the safety concerns highlighted by the so-called 'third generation pill scare' in Europe a decade ago. This scare heightened patient and physician awareness of the increased risk of thromboembolic complications (mainly venous thromboembolism [VTE]) associated with OC use.

Yasmin® (ethinylestradiol 30μg/drospirenone 3mg [EE/DRSP]) is a novel OC that was demonstrated in clinical phase I–III studies to be highly effective in preventing pregnancy and to have a good safety profile. Nonetheless, clinical trials are not usually sufficiently powered to detect rare adverse events such as VTE to enable comparison with other OCs, which could allay fears and concerns

about their inherent risks. Therefore, an extensive assessment of the VTE risk associated with EE/DRSP has been undertaken by reviewing data from the clinical development programme, postmarketing surveillance and spontaneous worldwide reporting, as well as information from other sources.

Spontaneous worldwide reporting has revealed a VTE reporting rate of 5.1/100 000 women-years with EE/DRSP use. In contrast, 3-year interim results from a large, controlled, prospective postmarketing surveillance study suggest a VTE rate of 61/100 000 women-years for EE/DRSP, which is similar to the rates of 60/100 000 and 73/100 000 women-years for levonorgestrel-containing OCs and other OCs, respectively. When placed in context with potential biases and confounding factors that would inflate the perceived risk of VTEs with a novel OC, the VTE rate with EE/DRSP does not highlight any safety concerns. Furthermore, the risk of VTE with EE/DRSP or other OCs is far less than that associated with pregnancy and delivery (up to 800/100 000 women-years) or than other risks of daily living.

Available data indicate that EE/DRSP is not associated with any increased risk of other serious adverse events such as hyperkalaemia, cardiac arrhythmia or birth defects. Nonetheless, caution should be exerted in prescribing EE/DRSP to women with conditions that predispose to hyperkalaemia.

Overall, the safety data with EE/DRSP and other OCs indicate that these products have no negative impact on the risk of VTE (and other adverse events) in women who receive OCs for contraception.

Since their introduction in the 1960s, oral contraceptives (OCs) have become a popular form of reversible birth control among women. The safety profile of OCs has improved over the years with the reduction in the doses of estrogen and progestogen used, as well as the introduction of progestogens that closely resemble natural progesterone. However, there have been continuing concerns about adverse effects. In the mid-1990s, the increased risk of venous thromboembolism (VTE) seen in women taking OCs was primarily discussed for OCs containing new 'third-generation' progestogens (desogestrel and gestodene). Although an increased risk of VTE had been linked with OCs since the 1960s, and in particular was associated with the dose of estrogen, the newer third-generation progestogen-containing pills appeared to carry a higher risk than the older formulations ('third-generation pill scare'). Whether this risk is real or the result of biases and confounding factors is the subject of ongoing and vehement scientific debate.[1-8]

As a class, estrogen-containing OCs, as well as hormone-replacement therapy (HRT) products, increase the risk of VTE[9] and probably also the risk of arterial thromboembolism (ATE).[10] VTE in the form of deep venous thrombosis or pulmonary embolism may have severe clinical consequences; however, most cases of VTE present with minimal symptoms. In a prospective study of 2177 long-haul flight passengers or non-travelling controls, only 3 of 39 subjects with venous thrombosis, as detected by venous compression ultrasonography, were symptomatic (isolated calf pain).[11] This observation supports the notion that VTE may be substantially underdiagnosed in the general population.

In contrast, the widespread awareness of the link between VTE and OC usage may result in VTE being selectively more frequently identified in users of these products ('detection bias'). Given the scientific and public discussion on the VTE risk associated with third-generation OCs, this effect appears to be more pronounced in users of any new or innovative OC. In addition, the increased awareness of OC-

associated VTE has the effect that health professionals may assume a causal link and are therefore more likely to spontaneously report cases of VTEs to health authorities and/or pharmaceutical companies when they occur.

In 1999, in response to the third-generation pill scare, the Centre for Epidemiology & Health Research Berlin (ZEG), Berlin, Germany proposed to OC manufacturers that they should sponsor postmarketing, prospective, comparative safety surveillance studies when launching new preparations containing either a new progestogen and/or estrogen. The proposal by ZEG was based on the fact that robust safety data were not available at the time of this 'pill scare' that could have either substantiated or refuted the higher VTE risk with OCs containing the newer progestogens, even though some of the preparations had been marketed for several years. Such rigorous safety standards should be applied to all novel OCs so that safety data are available as soon as possible after launch.

Only one OC containing a new chemical entity has been submitted for regulatory approval since the proposal by ZEG was made. This novel OC contains ethinylestradiol 30μg in combination with the novel progestogen drospirenone 3mg (EE/DRSP) and is marketed as Yasmin® (currently available in more than 50 countries).[1,2] ZEG approached the manufacturer of Yasmin® (Schering AG, Berlin, Germany) with proposals to conduct an active surveillance study and to compare its safety profile with other established OCs, in particular those containing levonorgestrel. As a result, the EURAS (EURopean Active Surveillance) study was initiated in 2001. Recruitment of approximately 60 000 women is expected with follow-up anticipated to be completed by 2006. An independent advisory council was formed to impartially govern the study and ensure the safety of the study participants. Details of the EURAS study have been presented elsewhere.[12-14]

Although the EURAS study was triggered by the experience of the 'pill scare', a risk management programme for a new chemical entity like drospirenone cannot concentrate only on the risk of VTE. Therefore, the risk management programme to monitor the safety of EE/DRSP was built around finding answers to three main questions: (i) What are the potential risks? (ii) Are these risks real? (iii) If there are real risks, why do they exist? These questions should be addressed sequentially. A careful analysis of the first question is the basis of an adequately designed study that could then answer the second question. Moreover, premature investigation of the third question may lead to the explanation of a phenomenon that does not exist.

To address the first question, the pharmacology of drospirenone, as well as the regulatory environment and public perception of OC safety, needs to be considered. In times of rapidly advancing specialisation in medicine where even specialised physicians may lack in-depth understanding of all subdisciplines of their area of expertise, the public has the legitimate need of reassurance of the safety of new drugs. Without an adequate risk management programme that provides early answers to public safety issues, even the unsubstantiated or perceived suspicion of a risk may lead to public reactions in the mass media that force regulators and pharmaceutical manufacturers to restrict or prohibit the use of a drug.

Furthermore, the perception of a specific benefit of an OC may lead to preferential prescribing to high-risk patients.[15-19] This is particularly relevant for EE/DRSP as, based on the antimineralocorticoid and antiandrogenic properties of drospirenone,[20,21] preferential prescribing to obese women or women with acne, polycystic ovary syndrome, hypertension, premenstrual syndrome or premenstrual dysphoric disorder has to be considered. As these conditions are associated with a higher risk of VTE and ATE, as well as depression and eating disorders, a resulting higher incidence of adverse events may be due to higher baseline risk factors rather than a pharmacological effect of drospirenone. In this situation, it is essential to have comprehensive documentation of a patient's baseline characteristics. Fi-

1 The use of trade names is for product identification purposes only and does not imply endorsement.
2 In Germany also marketed as Petibelle®.

nally, perceived risks of a drug may lead to a high reporting rate of suspected adverse events through selective diagnosing and selective reporting.[22-24] In this regard, because of the antimineralocorticoid properties of drospirenone, the potential for an increased risk of hyperkalaemia and subsequent arrhythmia is as relevant as the potential for an increased risk of VTE, given the history of the pill scare.

This article reviews the safety profile of EE/DRSP-containing OCs, with an emphasis on the risk of VTE compared with other OCs. This predominately includes a discussion of interim data from the EURAS study (as of 9 June 2004, based on follow-up data on 49 342 women) and the preliminary results from a phase IV study conducted in the US (as of 30 April 2004, based on follow-up data on 72 639 women) – findings that are published here for the first time. Furthermore, data from the clinical trial development programme and spontaneous reporting information from Schering AG are used as supportive evidence to characterise the safety profile of EE/DRSP. In addition, data were obtained from a comprehensive MEDLINE search conducted for relevant English language articles since 1970 (search term 'drospirenone') on the safety of drospirenone-containing hormonal products with a focus on thromboembolic complications (particularly VTE). Additional references were identified from the reference lists of published articles. Searches were last updated 1 September 2004.

1. Evaluating the Risk of Venous Thromboembolism (VTE) and Arterial Thromboembolism

The evaluation of VTE risk associated with EE/DRSP is based on three levels of evidence: (i) indirect evidence from clinical trials in well defined populations; (ii) worldwide spontaneous adverse drug reaction (ADR) reports from health professionals; and (iii) an active, controlled, prospective postmarketing surveillance study.

1.1 Clinical Trials

VTEs in young women are rare and cannot be evaluated within a regular clinical development programme for market authorisation of an OC (see section 1.3.1). As part of the phase I–III clinical development programme for EE/DRSP, only one case of suspected VTE (which was not confirmed by an imaging procedure) was reported in >2300 women-years of treatment.

As a single suspected case of VTE does not allow the calculation of a reliable incidence rate, it is interesting to look at relevant data from postmenopausal women using HRT products who have an approximately 10-fold higher incidence of VTE than younger women using OCs.[4,25-27] In addition to the EE/DRSP OC, a new preparation containing drospirenone has been developed for HRT.[28-31] Angeliq® (Schering AG, Berlin, Germany) is a continuous combined HRT consisting of estradiol 1mg and drospirenone 2mg (estradiol/DRSP). Although there are clear limitations of extrapolating safety data from an HRT to an OC product – including age and risk profile differences of the test population and the use of different estrogens and doses of drospirenone – potential safety problems with a strong correlation to age (e.g. VTE) might be easier to detect in an older population. Therefore, the safety assessment of a DRSP-containing OC must consider the available evidence from drospirenone-containing HRT preparations.

In phase I–III studies of estradiol/DRSP almost 1900 women were treated for almost 2000 women-years (mean duration ~1 year).[32] During estradiol/DRSP treatment, four VTE-related events were reported, giving an event rate of 204/100 000 women-years (95% CI 56, 522). The VTE rate for the continuous combined comparator product in these trials, conjugated equine estrogens (0.625 mg/day) plus medroxyprogesterone (2.5 mg/day) [Prempro™], was more than 2.5-fold higher (571/100 000 women-years). However, this rate is based on one event out of 175 women-years and does not represent a reliable benchmark. Therefore, a comparison with VTE rates from other large-scale clinical trials was done.

The VTE rate observed with estradiol/DRSP is lower than that reported for Prempro™ (overall 340–590/100 000 women-years) in large-scale clinical trials such as the WHI (Women's Health Initiative) study[25] and the HERS (Heart and Estrogen/Progestin Replacement Study).[26] Of the large-scale trials, the WHI trial (n = 16 608 women) showed the lowest overall incidence of VTE of 340/100 000 women-years (95% CI 288, 400) over the mean follow-up period of 5.2 years. However, during the first year of HRT, the incidence of VTE was 580/100 000 women-years (95% CI 430, 768).

Because there may be methodology issues in comparing VTE rates for different HRT combinations across studies (e.g. different study population ages, different types and doses of estrogen, and different inclusion criteria), these findings should be interpreted with caution. Nevertheless, the estradiol/DRSP data show no evidence of an increased risk of VTE with drospirenone, compared with other estrogen/progestogen combinations.

Although the available evidence from clinical studies on EE/DRSP and estradiol/DRSP cannot be used to draw strong positive safety conclusions about the EE/DRSP OC preparation, what is important is that no safety signals were identified for drospirenone in this setting.

1.2 Spontaneous VTE Reporting Rates

The second level of evidence is derived from spontaneous reports from health professionals. Although spontaneous reports are the weakest level of evidence of the three considered in this review, they remain a form of evidence that must be monitored for safety signals. Spontaneous reporting is often the only source of data that regulators, the media and the public have from which they can identify safety signals. In this section, we present some of the limitations, biases and confounding variables that must be considered when monitoring spontaneous reporting data and attempt to put this level of evidence into better context.

During the period since the first launch of EE/DRSP to 6 January 2004, the exposure to it worldwide was 60 million cycles, which translates into 4.6 million women-years. The number of VTEs reported to Schering AG during this period was 235, currently giving a VTE rate of 5.1/100 000 women-years.[32] The incidence of VTE according to the European Medicines Agency (EMEA) for OCs as a class is 20–40/100 000 women-years.[33] However, these reporting rates cannot be compared directly as there are a number of biases and confounding factors that influence reporting rates, which are usually substantially lower than true incidence rates. With respect to EE/DRSP, this underreporting should be relatively low (as described in sections 1.2.1–1.2.4).

1.2.1 Increased VTE Risk: Duration of Use

As illustrated by the Transnational Study on Oral Contraceptives and the Health of Young Women,[34-36] the WHI study on HRT[25] and various meta-analyses,[7,8] the risk of VTE is maximal during the first year of use (3- to 4-fold increased risk), but subsequently declines with continued use (figure 1). Women who are susceptible to VTE probably experience a thrombosis soon after they start OC intake and then stop treatment. Therefore, a population of long-term users who do not switch between different preparations includes only a few high-risk patients and therefore has a low VTE rate.[35] In addition, greater diagnostic bias in the first years of use may contribute to the time course of diagnosed VTE.

Market research by Schering AG conducted in 2003 showed that about 50% of EE/DRSP users were currently in their first year of use.[32] This is in contrast to established levonorgestrel-containing OCs, where about 20% of women were found to be in their first year of use.[34] The first-year user effect, plus the increased willingness of health professionals to report adverse events for a new product, typically leads to increased reporting rates (i.e. low underreporting) in the first years of market introduction (figure 2).[32]

1.2.2 Public Awareness

Public awareness of a real or perceived risk can lead to a detection bias and increased reporting rates.[22-24] The impact of public awareness and greater VTE risk during the first year of use on EE/DRSP-related VTE reporting rates are represented

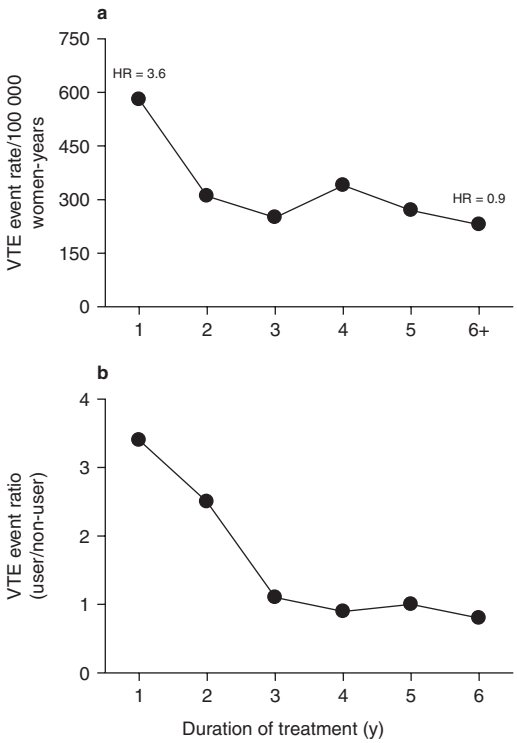

Fig. 1. Impact of duration of use of estrogen/progestogen combinations used for (**a**) hormone replacement therapy[25] or (**b**) oral contraceptives[35] on the risk of venous thromboembolism (VTE). **HR** = hazard ratio.

in figure 3. VTE reporting rates increased sharply soon after EE/DRSP was launched in different markets and after an episode of increased public awareness (following publication of a *British Medical Journal* article on VTE cases in The Netherlands[37]). In response to such events, there was initial enthusiasm by healthcare professionals to monitor and detect VTE episodes. However, this was followed by a decline in the VTE reporting rate, reflecting the limited interest by physicians to report these events after 6–12 months.

1.2.3 Preferential Prescribing to High-Risk Populations

Novel OCs are potentially preferentially prescribed to patients with a higher risk of VTE and to users who are dissatisfied with their current OC. In contrast, women who do not experience adverse effects with their current OC typically continue to use that preparation (usually a well established formulation).[15] These dissatisfied OC users also tend to switch selectively to the most recently marketed product.[15] This selective prescribing, coupled with pronounced detection bias, may result in an apparent successive increased risk associated with new products, as illustrated by the significant ($p = 0.00012$) linear trend in figure 4. These factors may partially explain the paradoxical VTE risk of Marvelon® (ethinylestradiol 30µg/desogestrel 150µg) compared with Marvelon 20® (ethinylestradiol 20µg/desogestrel 150µg) [figure 4]. Theoretically, the lower ethinylestradiol dose OC should have a lower VTE risk; in reality, however, a higher risk for VTE was reported. This discrepancy shows that other factors (e.g. selective prescribing to high-risk groups and/or detection bias) have a substantially higher impact on VTE reporting rates than do differences in OC formulation.

For EE/DRSP, there may be preferential prescribing to women who are obese or have mild hypertension, acne, polycystic ovarian syndrome, or eating or other psychiatric disorders. A tendency to prescribe a drospirenone-containing OC to these populations is based on the pharmacodynamic profile of drospirenone.[20,21] The antimineralocorticoid activity of drospirenone can counteract estrogen-induced mineralocorticoid effects such as retention of sodium, loss of potassium and the secondary

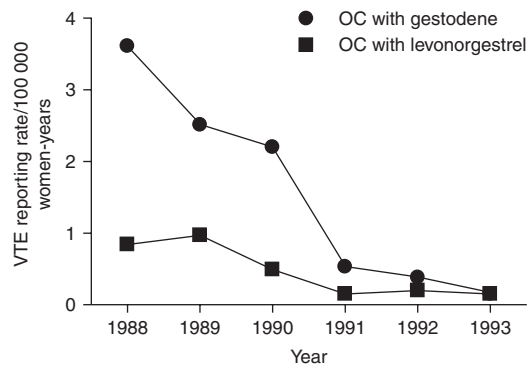

Fig. 2. Reporting rate of venous thromboembolism (VTE) during the first years of market introduction of a new oral contraceptive (OC) containing gestodene (introduced to market in 1987) or levonorgestrel (introduced in the early 1970s), illustrating the first-year user effect.[32]

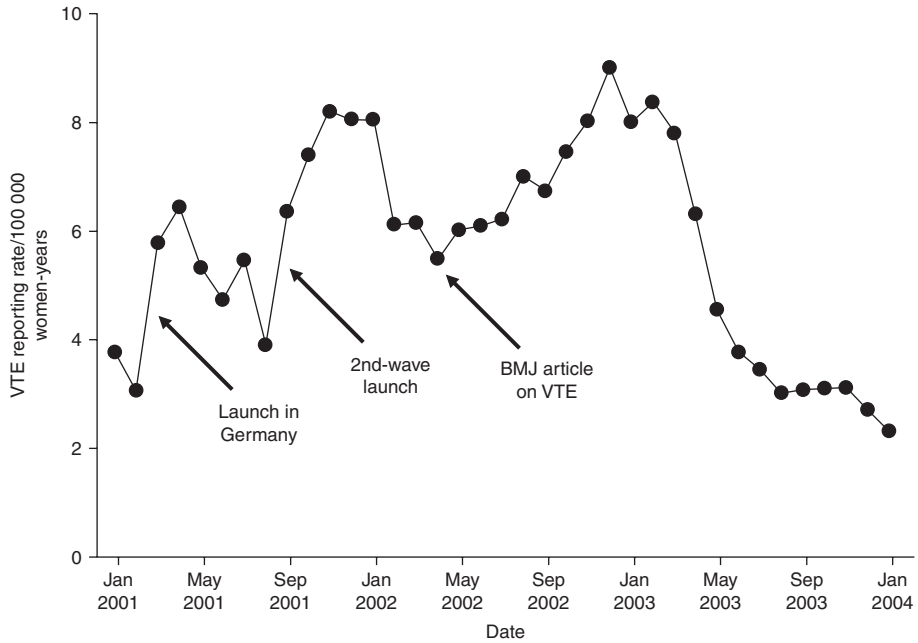

Fig. 3. Worldwide spontaneous reporting rate of venous thromboembolism (VTE) among ethinylestradiol/drospirenone users, depicting the impact of local market introductions and public awareness.[32] "2nd-wave launch" refers to launch in the US and the Nordic countries. The *British Medical Journal* (BMJ) article on VTE refers to Sheldon (2002).[37]

retention of water.[38,39] In susceptible women, estrogen effects may result in slightly increased blood pressure, weight gain, bloating and breast tenderness. In addition, the antiandrogenic activity of drospirenone can effectively reduce the severity of acne and seborrhoea,[40,41] with possible benefits on women with hirsutism and polycystic ovarian syndrome.[42] Based on the preferential prescribing of EE/DRSP to these women, many of whom have higher baseline risk factors (e.g. for VTE or other adverse effects),[43] an increased incidence of events including VTE and psychiatric disorders would not be unexpected with this OC.

1.2.4 Reporting Behaviour of Pharmaceutical Companies

The VTE reporting rate seems to be also dependent on the degree of proactive behaviour of pharmaceutical companies in encouraging and sensitising health professionals to report adverse events to regulatory agencies, either directly or via pharmaceutical companies. This has been demonstrated for the reporting rate for two identical OC formulations containing gestodene that were manufactured at the same site and launched at the same time, but marketed by different companies. There were marked differences between the two companies (factor of about 2) in reporting rates for all VTE events (2.5 vs 1.3/

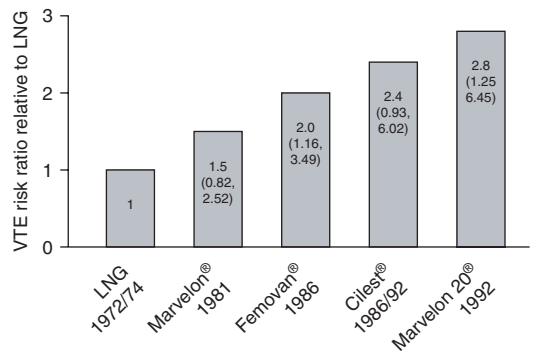

Fig. 4. Risk ratios (95% CI) of oral contraceptives containing various progestogens compared with levonorgestrel (LNG; reference treatment) by year of market introduction, illustrating the impact of preferential prescribing and diagnostic bias on the reporting rate of venous thromboembolism (VTE) [reproduced from Lewis et al.,[15] with permission from Elsevier].

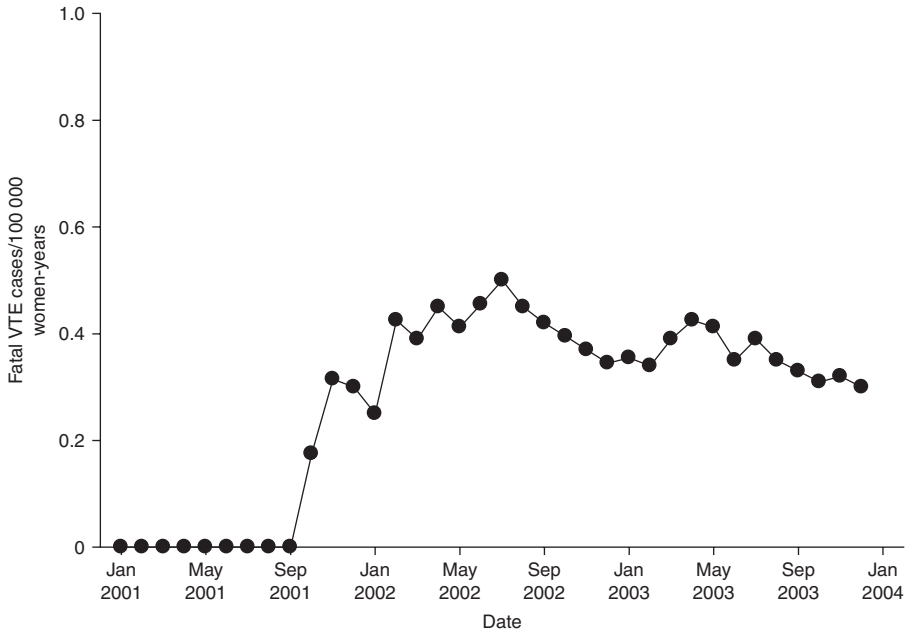

Fig. 5. Worldwide rate of fatal venous thromboembolism (VTE) among ethinylestradiol/drospirenone users.[32]

100 000 women-years) and for pulmonary embolism (1.3 vs 0.5/100 000 women-years).[44]

1.2.5 Estimation of Incidence Rates from Reporting Rates

For the reasons given in sections 1.2.1–1.2.4 we assume that VTE rates associated with EE/DRSP are not heavily underreported. Although spontaneous reporting can be considered a weak piece of evidence, it nonetheless may show a safety signal. Furthermore, spontaneous reporting often triggers a public safety discussion of a product, which requires careful scientific analysis of the potential biases. In the following paragraphs a rough semi-quantification of the underreporting is given to evaluate whether the spontaneous VTE reporting rate represents a safety signal.

In general, serious outcomes that occur during therapy tend to be more consistently reported than non-serious adverse events.[45,46] Fluctuations in reporting rates in response to product launches and media reporting (as shown in figure 3 for VTE) are only possible if an adverse event is underdiagnosed or underreported. If diagnosis or reporting is close to 100%, not even product launches and increased awareness have the potential to substantially increase reporting rates. The fact that reporting rates for fatal VTE, in contrast to general VTE reporting rates, during EE/DRSP use (compare figure 5 with figure 3) do not fluctuate considerably supports the assumption that fatal VTEs in young women using EE/DRSP are not heavily underreported. From these findings it is possible to roughly estimate the true incidence of VTE based on the reporting rate.

The true rate of fatal VTEs as a proportion of total VTEs reported has been estimated at 1.5%,[33] from which the degree of underreporting of VTEs can be estimated based on the assumption that the majority of fatal VTEs are reported in OC users. For example, with EE/DRSP the reported proportion of all VTE events that are fatal is 4.8%, which is 3.2 times higher than the true rate of 1.5%. In contrast, the reported proportion of fatal VTEs for Microgynon® (an ethinylestradiol/levonorgestrel OC marketed by Schering AG) is 26%, which is 17.3 times higher than the true rate of fatal VTE, according to Schering AG's ADR database. It is extremely unlikely that VTEs in ethinylestradiol/levonorgestrel users are more likely to be fatal than in EE/DRSP

users. Therefore, these simple calculations strongly suggest that VTE underreporting for EE/DRSP is much lower than that for established OCs. Furthermore, if 100% of fatal VTEs were reported, multiplying the worldwide EE/DRSP VTE rate of 5.1/100 000 women-years by the 3.2 underreporting factor results in a calculated VTE incidence rate of 16.3/100 000 women-years, which is lower than the VTE rate for other OCs (20–40/100 000 women-years).[33] Even if one assumes that only 50% of fatal VTEs in young women are reported, a reporting rate of 5.1/100 000 women-years would not indicate an increased VTE risk with EE/DRSP compared with other OCs.

1.3 Active Surveillance Studies

1.3.1 Detection of VTE: Sample Size Considerations

Significant differences in VTE risks between different OCs, as well as the absence of these risks, cannot be demonstrated in clinical trials because of the very low incidence (20–40/100 000 women-years) of these events and the relatively small sample size of clinical trials. Table I shows the total sample size that would be required to demonstrate non-inferiority in VTE risk of one OC versus another (or that the VTE risk of one OC is not higher than another), assuming that the true VTE rates are equal. Using standard settings for α and β, the required total sample size is dependent on three key considerations: the assumed VTE rate, the non-inferiority margin (which determines an unfavourable estimate of the relative risk that would still be considered not to establish non-inferiority) and withdrawal rates.

An assumed VTE rate of 20–40/100 000 women-years in OC users represents the incidence seen in epidemiological trials focusing primarily on hospitalised and/or idiopathic cases; this range is included as part of the European standard label for OCs.[33] However, a more accurate estimate of VTE rate in healthy women, derived from synthesis of data from clinical studies in Schering AG's database, suggests VTE rates of 52 and 65/100 000 women-years. The assumed VTE rate has considerable impact on study size: a rate of 20/100 000 women-years, compared with 65/100 000 women-years, necessitates a 3-fold larger study population.

Another important factor that influences study size is the selection of the non-inferiority margin (e.g. VTE rate/4, VTE rate, 2 × VTE rate), which can be translated into a relative risk (table I). For example, if a 25% higher point estimate (i.e. with a relative risk of 1.25) of the VTE rate were accepted as not being inferior, a minimum of 3 360 000 women completing 1 year of treatment would be necessary to show, with at least 90% power and a significance level of 5%, that the new OC is non-inferior to the reference OC. The acceptance of higher non-inferiority margins would decrease the number of women-years substantially. However, acceptance of study results by the public and regulators would decrease at the same time. From a legal point of view, a relative risk of two represents an important threshold:[48] a higher relative risk could be interpreted legally that an event would likely have not occurred with a standard OC.

A final factor that impacts on study size is the high withdrawal rate typically reported for OC trials

Table I. Sample size requirements[47] to show that a new oral contraceptive is no worse (non-inferior) than a reference oral contraceptive with regard to the rate of venous thromboembolism (VTE). Assumptions are: α = 5%; power = 90%; the true VTE rates associated with each treatment are equal; treatment duration per patient is 1 year

Assumed VTE rate per 100 000 WY	Total sample size (net)			
	δ = VTE rate/4	δ = VTE rate/2	δ = VTE rate	δ = 2 × VTE rate
20	3 360 000	840 000	210 000	53 000
40	1 680 000	420 000	105 000	26 000
52	1 290 000	320 000	82 000	21 000
65	1 030 000	260 000	65 000	17 000
Relative risk[a]	**1.25**	**1.5**	**2.0**	**3.0**

a Which determines an unfavourable estimate of the relative risk that would still be considered not to establish non-inferiority.

δ = non-inferiority margin; **WY** = women-years.

(in our experience ~30% within 1 year). OC studies involve women who are young and healthy; they typically do not have a disease that motivates them to stay in a trial. Instead, changes in their personal situation, such as a new partner, may alter their need for contraception. Also, as women in this demographic often move from one geographic location to another and/or change their physician, vigilant follow-up for information is essential. The expected withdrawal rate has to be added to the figures shown in table I.

It is practically impossible to conduct a clinical trial of sufficient size and power to demonstrate that one OC is no worse than another with respect to VTE rates. This is one important reason why observational studies are necessary. However, their results are meaningful only if the study is powered to exclude at least a 2-fold VTE risk with test treatment as being not higher than reference treatment and if the number of women from whom follow-up information (e.g. about serious adverse events) is unavailable can be limited to the absolute minimum.

1.3.2 The EURAS Study

The EURAS study is a multinational, controlled, prospective, postmarketing observational study of new users of EE/DRSP or other OCs.[12] The planned exposure (>100 000 women-years in three cohorts) is sufficient to detect a relative risk of two at an assumed VTE rate of 65/100 000 women-years (table I). Strong efforts are made to minimise the number of women who are lost to follow-up (e.g. search for family members and friends, searching public registers). Complete details of the EURAS study protocol and endpoints have been published elsewhere.[12,13] Briefly, women starting OC treatment (first-ever user or switching from another product) were actively monitored for the occurrence of rare or unexpected adverse outcomes possibly related to OC exposure. Only the salient results of an interim analysis are reported in this publication as unpublished observations.

On 9 June 2004, total enrolment for all participating centres (over 1000 in seven European countries: Austria, Belgium, Denmark, France, Germany, The Netherlands and the UK) was more than 55 000 women. At this timepoint, follow-up information for 49 342 women was available, yielding 64 103 women-years of observation (>830 000 cycles). Of these women, 30.4% were using EE/DRSP, with 29.7% and 39.9% using levonorgestrel-containing OCs or other OCs, respectively (table II). The mean age and disposition of risk factors (except for body mass index [BMI] >30 mg/m^2 and cholesterol levels) at baseline were similar for all three user cohorts. There was a greater proportion of women in the EE/DRSP cohort with a BMI >30 mg/m^2 (7.0%) compared with the other OC (3.7%) and levonorgestrel-containing OC cohorts (4.4%). There was a similar trend for high (i.e. above the upper normal limit of the local laboratory) cholesterol levels: a greater proportion of EE/DRSP users (3.0%) had elevated cholesterol levels versus users of other OCs (2.4%) or levonorgestrel-containing OCs (1.8%). Given the risk profile of users in the EE/DRSP cohort and association of these two risk factors with increased VTE risk, a small increase in VTE might be expected in these users, compared with other OCs.

Two hundred and five VTE-like events were self-reported, of which 163 were ruled out because of patient misunderstanding. The remaining 42 cases were confirmed as a definite VTE (by an imaging procedure) or as a probable VTE (by clinical diagnosis or a non-imaging procedure). The VTE event rate in the EE/DRSP cohort was similar to that in the

Table II. Details of each oral contraceptive (OC) user cohort in the EURAS (EURopean Active Surveillance) study

Parameter	OC user cohort			
	EE/DRSP	Levonorgestrel-containing OCs	Other OCs	Total study
No. of users (%)	15 020 (30.4)	14 630 (29.7)	19 692 (39.9)	49 342 (100)
Women-years (%)	19 530 (30.5)	18 476 (28.8)	26 097 (40.7)	64 102 (100)
Mean age (SD) [y]	26.3 (8.2)	25.2 (8.8)	25.1 (8.0)	25.5 (8.3)

EE/DRSP = ethinylestradiol/drospirenone; **SD** = standard deviation.

Table III. Confirmed thromboembolic adverse events in the EURAS (EURopean Active Surveillance) study

Event category	EE/DRSP cohort		Levonorgestrel-containing OCs cohort		Other OCs cohort		Total study (n)
	n	per 100 000 WY (95% CI)	n	per 100 000 WY (95% CI)	n	per 100 000 WY (95% CI)	
No. of VTE/ATE	13	67 (35, 114)	14	76 (41, 127)	23	88 (56, 132)	50
Total no. of VTE	12	61 (32, 107)	11	60 (30, 107)	19	73 (44, 114)	42
no. of PE only	3	15 (3, 45)	2	11 (1, 39)	2	8 (1, 28)	7
Total no. of ATE	1	5 (0, 29)	3	16 (3, 48)	4	15 (4, 39)	8
no. of AMI only	0	0 (0, 19)	1	5 (0, 30)	2	8 (1, 28)	3
no. of CVA only	1	5 (0, 29)	2	11 (1, 39)	2	8 (1, 28)	5
No. of fatal VTE/ATE	0	0 (0, 19)	2[a]	11 (1, 39)	0	0 (0, 14)	2

a One myocardial infarction (directly linked to OC use) and one VTE (indirectly linked to OC use: this woman died from therapy-resistant hepatic failure after liver transplantation; the hepatic failure was possibly due to a toxic reaction to long-term VTE anticoagulation therapy).

AMI = acute myocardial infarctions; **ATE** = arterial thromboembolisms; **CVA** = cerebrovascular accidents (stroke); **EE/DRSP** = ethinylestradiol/drospirenone; **OC** = oral contraceptive; **PE** = pulmonary embolisms; **VTE** = venous thromboembolisms; **WY** = women-years.

levonorgestrel-containing OC and other OC cohorts, with incidences of 61, 60 and 73/100 000 women-years (table III). There were no statistically significant differences between the cohorts. The hazard ratios for the VTE risks determined by Cox regression analysis adjusted for age, BMI, duration of use and VTE history were 1 (95% CI 0.43, 2.29) for EE/DRSP versus levonorgestrel-containing OCs and 0.86 (95% CI 0.4, 1.85) for EE/DRSP versus other OCs.

Overall, 50 thromboembolic events (VTE and ATE) were confirmed in the study. The incidence of all VTE and ATE events was highest in the other OC user cohort when compared with EE/DRSP and levonorgestrel-containing OC users (table III), although there were no significant differences between groups. For all thromboembolic events, the hazard ratio for EE/DRSP versus other OCs was 0.75 (95% CI 0.37, 1.51); the ratio versus levonorgestrel-containing OCs was 0.93 (95% CI 0.44, 1.99). These results suggest that EE/DRSP does not increase the rate of thromboembolic events compared with other OCs.

A notable finding from the EURAS data is that the majority of VTEs (38 of 42) occurred in users who had switched from one OC to another. These users represent ~80% of all study participants; the remaining ~20% were first-time OC users (starters). The incidence of VTE in switchers was 73/100 000 women-years. Even if the higher average age of switchers is considered, these data suggest that switchers have a similar risk of thromboembolic events when compared with first-ever users. These findings are in line with previous findings,[36] which indicate that switchers have a substantially higher risk than long-term users of one product.

VTE reporting rates for OCs are usually highest during the first year of use. Results from the EURAS study for EE/DRSP indicate a similar trend, with approximately 3-fold more VTEs reported after the first year versus 3 years of follow-up (figure 6). Another important finding was that obese women (BMI ≥30) had a more than 4-fold VTE risk compared with women with normal weight (BMI

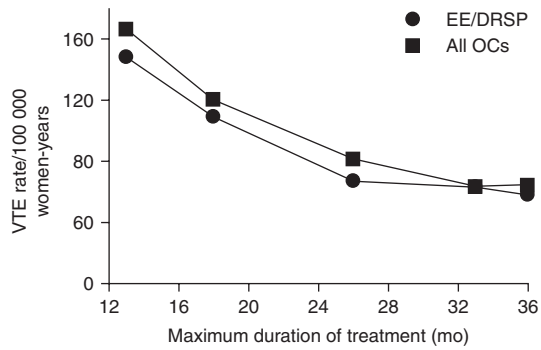

Fig. 6. Time-dependent decline of the rate of venous thromboembolism (VTE) in the ethinylestradiol/drospirenone (EE/DRSP) and all oral contraceptives (OCs) user cohorts in the EURAS (EUROpean Active Surveillance) study.

20.0–24.9) and a more than 10-fold risk compared with slim women (BMI <20). A more detailed analysis of these trends will be conducted at the end of the study. Given these findings, comparison of VTE results from one study with another is only possible if exact information for duration of use and time after market introduction, as well as for baseline characteristics of the population (e.g. age and BMI), is available.

Despite the slightly higher proportion of high-risk women in the EE/DRSP cohort, users of this OC were not at an increased risk of VTE or ATE compared with other preparations. Therefore, the 3-year interim findings of the EURAS study, consistent with data from clinical trials and from worldwide spontaneous reporting rates, indicate that EE/DRSP does not increase the risk of VTE or ATE compared with other OCs.

2. Hyperkalaemia and Arrhythmia

Drospirenone is an analogue of spironolactone and as such has antimineralocorticoid properties; drospirenone 3mg is comparable to spironolactone 20–25mg in terms of the magnitude of the antimineralocorticoid effects. As a consequence, there is a theoretical potential for hyperkalaemia to develop in some women who take an oral formulation containing drospirenone, particularly when drospirenone-containing formulations are co-administered with potassium-sparing agents in patients with severe renal insufficiency. Information on the safety of drospirenone and drospirenone-containing formulations with regard to hyperkalaemia (and associated subsequent arrhythmia) has been obtained from several sources. These include the US phase IV study, the EURAS study and the EE/DRSP clinical trial programme. Moreover, spontaneous reports of adverse events are also being screened to identify hyperkalaemia and arrhythmia events.

2.1 US Phase IV Study

As a part of a risk management programme required by the US FDA, a phase IV claims database observational cohort study was initiated at the time of introduction of Yasmin® to the US market in June 2001. Specifically, subsequent outcomes of death, hospitalisation, syncope, arrhythmia, hyperkalaemia and other adverse events are being investigated. The claims data are from UnitedHealthcare, the second largest healthcare provider in the US. The UnitedHealthcare Research Database contains information from more than 20 affiliated health plans located in the northeast, southeast, midwest and western US. Beginning with the earliest claims, in 1990, the Research Database has information on approximately 8 million current and past members.

Women prescribed EE/DRSP were identified through pharmacy dispensing records. For comparison, women were selected from among those who received other OCs, but were otherwise similar to EE/DRSP users. The EE/DRSP and comparison groups were balanced with respect to a wide variety of demographic, health and healthcare utilisation characteristics using propensity scores. Overall, about 34 000 users of EE/DRSP and about 68 000 users of other OCs from patients identified between June 2001 to June 2004 will be matched. Presented results are based on a validation of 23 915 users of EE/DRSP and 48 724 users of other OCs (June 2001 to 30 April 2004).

The results for the incidence of hyperkalaemia, electrolyte disturbance and associated adverse events for the cohort of women identified are presented in table IV. No cases of hyperkalaemia were reported for the EE/DRSP group compared with a rate of 15/100 000 women-years in the other OC group. The reporting rate of arrhythmia was similar for EE/DRSP compared with other OC users. In addition, there were fewer reports of events potentially related to hyperkalaemia (e.g. electrolyte disturbances, syncope) with EE/DRSP versus other OCs.

2.2 EE/DRSP Clinical Assessment Programme

Potassium levels were extensively measured as part of the phase I–III clinical programme for EE/DRSP. Moreover, the risk of hyperkalaemia from drospirenone was also investigated in high-risk populations (e.g. those using other potassium-sparing drugs or with renal insufficiency) or after admin-

Table IV. Incidence (events/100 000 women-years) of hyperkalaemia, electrolyte disturbance, syncope and arrhythmia in users of ethinylestradiol/drospirenone (EE/DRSP) and users of other oral contraceptives (OCs) in an ongoing US phase IV study based on the UnitedHealthcare Research Database

Event	EE/DRSP		Other OCs		Rate ratio
	n	incidence (95% CI)	n	incidence (95% CI)	(95% CI)
Hyperkalaemia	0	0 (0, 54)	2	15 (2, 54)	0 (0, 11.5)
Arrhythmia	13	204 (109, 348)	27	196 (129, 285)	1 (0.5, 2.1)
Syncope	19	298 (179, 466)	56	406 (307, 527)	0.7 (0.4, 1.3)
Electrolyte disturbance	6	94 (34, 205)	25	181 (117, 267)	0.5 (0.2, 1.3)

EE/DRSP = ethinylestradiol/drospirenone; **OC** = oral contraceptive.

istration of acute overdose (single doses of drospirenone up to 100mg).[32] The clinical assessment programme included two studies investigating the interaction between estradiol 1mg/drospirenone 3mg and either the potassium-sparing drug indomethacin (17-day administration in healthy postmenopausal women) or the ACE inhibitor enalapril (enalapril maleate) [14-day administration in mildly hypertensive postmenopausal women].[49] Another trial involving 14-day treatment with drospirenone 3mg in non-hospitalised women (aged 18–75 years) with normal (>80 mL/min), mild (50–80 mL/min) or moderate (30–50 mL/min) creatinine clearance was also performed (unpublished data).

Results from the entire clinical phase I–III programme for EE/DRSP support the lack of effect of this OC on potassium levels. In phase III studies, 98.2% of 3113 potassium measurements (from 1151 women) were within the normal range; this figure compares with 97.4% for EE/desogestrel (1714 potassium measurements from 596 women). Additionally, there was no increased risk of hyperkalaemia with drospirenone or drospirenone-containing preparations in studies involving high hyperkalaemia risk populations (e.g. taking co-medication or with renal insufficiency) or following acute drospirenone overdose.

2.3 Spontaneous Reporting of Hyperkalaemia

A total of 15 cases of hyperkalaemia or serum potassium increase with EE/DRSP have been reported to Schering AG, giving a reporting rate of 3.3 per million women-years.[32] However, none of these cases was serious and the highest reported serum potassium level was 5.6 mmol/L; this increase does not represent severe hyperkalaemia and should not result in any cardiac symptoms. Accordingly, arrhythmia was not reported in any of these cases. The very low reporting rate is consistent with (or even lower than) the reporting rates seen for other OCs in the Schering ADR database and suggests that EE/DRSP users have no increased risk of hyperkalaemia or hyperkalaemia-induced arrhythmia. No case reports for EE/DRSP had been reported in the literature as of September 2004.

2.4 The EURAS Study

A final piece of evidence that the risk of arrhythmia with EE/DRSP is not increased is provided by the 3-year interim results from the EURAS study. The rates of reported arrhythmia for EE/DRSP, levonorgestrel-containing OCs and other OCs were 1049, 960 and 1041/100 000 women-years, respectively. Most of the reported cases were already present at baseline or could not be confirmed by ECGs. There were no relevant differences in the rate of new occurrences of arrhythmia (which includes worsening of pre-existing conditions) among users of EE/DRSP (49/100 000 women-years), levonorgestrel-containing OCs (57/100 000 women-years) and other OCs (45/100 000 women-years).

3. Other Safety Aspects of EE/DRSP

Investigation of other serious ADRs (e.g. those leading to fatalities, psychiatric disorders or congenital malformations in children conceived during EE/DRSP use) with EE/DRSP and other OCs was integral to the clinical assessment of EE/DRSP. All

serious events from the EURAS and the US phase IV studies recorded to date have been validated and fully documented. Furthermore, all spontaneous reports of adverse events with EE/DRSP have been screened for indicators of other potential risks.

The overall adverse event rates from the EURAS study in the EE/DRSP, levonorgestrel-containing OC and other OC user cohorts were 878, 918 and 907/10 000 women-years. These values are very similar and do not indicate any difference between the products. Furthermore, the EURAS patient questionnaires were used in a survey of 19 960 women aged 15–44 years to investigate the overall adverse event rate in a representative sample of the female population in Germany. The rate of adverse events in this population was of the same order of magnitude as that seen in the three OC cohorts (+18%) [a full analysis of this survey will be published separately]. These results indicate that VTEs represent <1% of all reported events and that the overall event rates seen in the EURAS study are comparable to those seen in a general female population of the same age, supporting the notion that OCs have no negative impact on public health.

3.1 Fatal Outcomes

Based on spontaneous reporting, the overall worldwide mortality rate related to VTE among EE/DRSP users is in the order of 0.2–0.5/100 000 women-years. This rate is lower than the mortality rate of 1.4/100 000 women-years from the Danish Health Registers in a general female population (users and non-users of OCs) matched to the age profile of EE/DRSP users.[50] Therefore, the EE/DRSP OC does not appear to have a negative impact on VTE-related mortality rates.

In the EURAS study, there have been two deaths in the EE/DRSP cohort and eight deaths in the other two cohorts; this equates to ten deaths during approximately 64 000 women-years, corresponding to a rate of 16/100 000 women-years. The two fatalities in the EE/DRSP cohort in the EURAS study were due to rupture of an aortic aneurysm in one case and liver failure in the other case (due to liver metastasis from a neuroendocrine cancer). Causality assessment by the treating physician concluded that there was no causal relationship between the fatalities and EE/DRSP.

The mortality rate observed in the EURAS study (16/100 000 women-years for all and 10/100 000 in the EE/DRSP cohort) is lower than the age-matched mortality rate of 43/100 000 women-years reported in a general population of Danish women.[50] These findings are in line with the well known net beneficial effect of OC use on mortality, when mortality associated with pregnancy, delivery and abortion in non-OC users is taken into account. A final consideration is the healthy user effect: women in good health are more likely to use an OC than women with health problems.[23]

3.2 Psychiatric Disorders

The most frequently reported psychiatric disorders among all three user cohorts in the EURAS study that led to hospitalisation were depression (23 cases), eating disorders (six cases) and abnormal stress reaction (six cases). The incidence of total psychiatric disorders was lowest in the EE/DRSP cohort (49/100 000 women-years) compared with the levonorgestrel-containing OC cohort (71/100 000 women-years) and other OC user cohort (104/100 000 women-years). This trend was also observed for the incidence of individual psychiatric disorders. These results suggest that EE/DRSP has no unfavourable impact on psychiatric disorders leading to hospitalisation.

3.3 Birth Defects

Like all modern OC preparations, EE/DRSP and all other OCs used in the EURAS study were effective forms of contraception. The lowest numbers of unwanted pregnancies were reported in the EE/DRSP and the other OC cohorts (unadjusted Pearl Index [PI; expressed as pregnancies per 100 women-years of use] = 0.3), compared with users of levonorgestrel-containing OCs (PI = 0.4). For those women who became pregnant while using EE/DRSP in the EURAS and US phase IV studies, no fetal malformations were reported.

4. Conclusions

Extensive safety assessment is necessary for all new chemical entities. In the case of EE/DRSP, a risk management programme was developed to determine the potential risks of this novel OC. This safety programme was based on three levels of evidence: clinical trial data, spontaneous reporting and the two large postmarketing surveillance studies in Europe and the US. The safety assessment considered all serious adverse events with EE/DRSP, with an emphasis on the risk of thromboembolic events (e.g. VTE and ATE), fatalities, hyperkalaemia and arrhythmia, psychiatric disorders and birth defects.

A number of issues must be considered with regard to the incidence of VTE with EE/DRSP. The spontaneous VTE reporting rate of 5.1/100 000 women-years with EE/DRSP is a factor of 4–8 lower than the incidence given in the European standard label for OCs, despite increased awareness, first-year-of-use effect and high reporting rates. This first-year user effect cannot be underestimated and these relatively low spontaneous VTE reporting rates with EE/DRSP have been confirmed in the EURAS postmarketing surveillance study, based on an interim analysis of more than 49 000 women. Although the data for EE/DRSP in this study show a slight tendency towards a lower thromboembolic risk compared with other OCs, this result is probably due to chance. Nevertheless, it should be noted that the data are considerably robust and – as demonstrated in table I – even a 2- to 3-fold increase in exposure would not enable much better precision of the risk estimates.

An aspect of the EURAS data that may give rise to concern is that the incidence of VTE seen in all user cohorts (60–73/100 000 women-years) is higher than the rates given in the European standard label for OCs (20–40/100 000 women-years).[33] However, the EMEA figures are primarily based on studies of idiopathic VTE and/or of hospitalised cases; in contrast, as the EURAS cohort study includes all confirmed VTE cases, including non-idiopathic and non-hospitalised VTE, the overall incidence is expected to be markedly higher.[23] Furthermore, it has to be considered that VTEs are underdiagnosed and the substantial impact of diagnostic bias on VTE reporting cannot be understated.[11] With modern imaging techniques and the D-dimer assay that are currently available, it is considerably easier for a physician to confirm or exclude a VTE diagnosis; therefore, the number of VTEs diagnosed is rate limited by the availability of

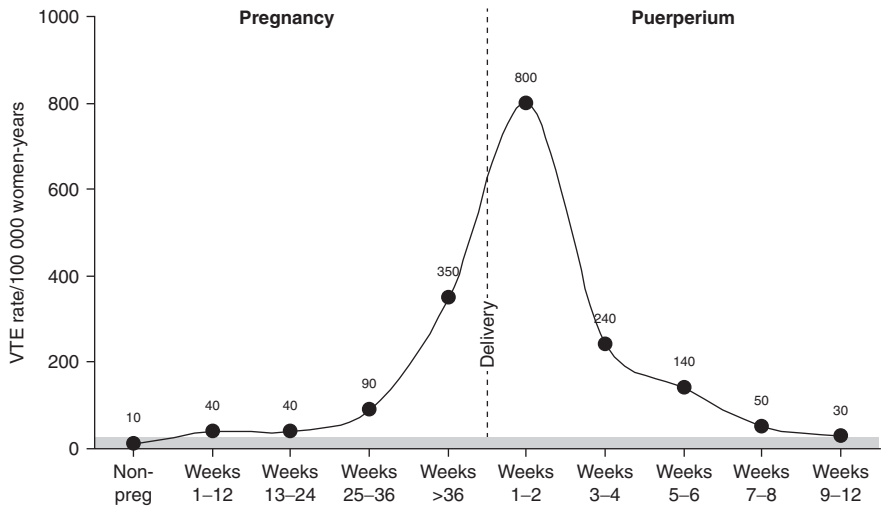

Fig. 7. Incidence of venous thromboembolism in non-pregnant (non-preg), pregnant and puerperal women. Data from the Danish Health Registers, 1994–1996 (n = 265).[50] The shaded bar represents the range of event rates typically associated with oral contraceptive use (reproduced from Lidegaard,[53] with permission).

diagnostic procedures and how frequently they are conducted.

Most cases of VTE are not diagnosed, and the incidence for non-OC users given in the European standard label (5–10/100 000 women-years) is probably much too low.[51,52] Given physicians' awareness about VTE in OC users, it is likely that the rate ratio of 4 between users and non-users (as given in the European standard label)[33] is an overestimate. However, the extent of this overestimation is difficult to determine. Moreover, direct comparison of the VTE rate for OC users with non-OC users should take into account that non-user data refer only to non-pregnant women and do not include the high VTE risk associated with pregnancy, abortion and delivery. OCs are predominantly prescribed to women who are at 'risk' of becoming pregnant. Therefore, any comparison of VTE risk should include the risks associated with pregnancy, delivery and abortion (figure 7).

Irrespective of the specific risk of VTE with OCs, it is helpful to put the absolute risk into perspective. The VTE rate as reported by the EURAS study for EE/DRSP or by the EMEA[33] for OCs (20–73/100 000 women-years) is comparable to the rate (per 100 000 women-years in a female population of the same age) of pedestrian and cyclist injuries that required hospital attention (60–177)[54] but less than the rate of sustaining injury in a motor vehicle (1035)[54] or of major gastrointestinal tract bleeding events in aspirin users (3640).[55,56]

There was no increased risk of clinically significant hyperkalaemia with drospirenone or drospirenone-containing preparations based on studies involving high hyperkalaemia risk populations (e.g. those taking co-medication or with renal insufficiency), spontaneous reporting or in the postmarketing surveillance studies. Nonetheless, caution should be exerted in prescribing EE/DRSP to women with conditions that predispose to hyperkalaemia. Additionally, there is no evidence to suggest that EE/DRSP leads to increased fatalities, psychiatric disorders or fetal malformations compared with other OCs.

Finally, the VTE rates seen with EE/DRSP and other OCs should not impact negatively on the VTE rate of the general female population up to the age of 45 years. Moreover, the risk of VTE with all OCs is not high compared with other risks encountered through daily living. The risk of VTE should not preclude prescription of EE/DRSP or other OCs for contraception to women with no known risk factors for VTE.

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