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Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonorgestrel: a meta-analysis and formal sensitivity analysis☆

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Abstract

Controversy exists regarding whether oral contraceptives (OCs) containing desogestrel and gestodene are associated with an increased risk of venous thromboembolism (VTE) versus OCs containing levonorgestrel. We were interested in synthesizing the available data, exploring explanations for mixed results, and characterizing the degree of uncontrolled confounding that could have produced a spurious association.

We performed a meta-analysis and formal sensitivity analysis of studies that examined the relative risk of VTE for desogestrel and gestodene versus levonorgestrel. Twelve studies, all observational, were included. The summary relative risk (95% CI) was 1.7 (1.3–2.1; heterogeneity $p = 0.09$). If real, the incremental risk of VTE would be about 11 per 100,000 women per year. An association was present when accounting for duration of use and when restricted to the first year of use in new users. However, in the sensitivity analysis, the association abated in many, but not all, scenarios in which an unmeasured confounding factor increased the risk of VTE three to fivefold and in nearly all examined scenarios in which the factor increased the risk 10-fold.

The summary relative risk of 1.7 does not appear to be caused by depletion of susceptibles, but is sensitive to a modest degree of unmeasured confounding. Whether such confounding occurred is unknown. However, given this sensitivity, this issue probably cannot be settled unequivocally with observational data. In the absence of a definitive answer, this apparent increased risk, together with its uncertainty and small magnitude and its important consequences, should be considered when selecting an OC for a given woman. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Oral contraceptives; Venous thromboembolism; Gestodene; Desogestrel; Levonorgestrel; Meta-analysis

1. Introduction

Oral contraceptives (OCs) have been used since the 1960s and are currently taken by approximately 100 million women worldwide [1]. Desogestrel- and gestodene-containing OCs (sometimes called third generation OCs) were introduced in Europe in 1981 and 1987, respectively [2,3].

In 1995, data began to emerge from observational studies suggesting that desogestrel and gestodene may be associated with a higher risk of pulmonary embolism and deep vein thrombosis (collectively referred to as venous thromboembolism or VTE) than were OCs containing levonorgestrel with comparable amounts of ethinyl estradiol (EE). However, as additional data and re-analyses emerged, these results were not always replicated.

The likelihood of a cause-effect relationship has been the subject of protracted debate. As summarized elsewhere [4–6], the most plausible arguments that the observed associations are spurious take two related forms. The first is that the association is due to unmeasured confounding. Confounding is the presence of a factor that is associated both with the exposure of interest (in this case, the selection

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☆ Supported by a research contract from Wyeth-Ayerst Research. The sponsor was given the opportunity to provide nonbinding comments on the manuscript. The authors retained publication rights, including freedom to determine the final wording.

of an OC containing desogestrel or gestodene rather than levonorgestrel) and with the outcome of interest (in this case, VTE). To have affected the study results, a confounder would need to have been inadequately adjusted for in the studies showing an association. For example, if third generation OCs were preferentially prescribed to women who, because of factors not adequately adjusted for, were at an increased risk of VTE, then these agents would be associated with VTE even if there were no cause-effect relationship. This concern is often referred to as “selection bias,” “prescription bias,” “confounding by indication,” or “channeling.” [4–8]. The degree of unmeasured confounding that could have produced the observed associations has not been formally characterized.

A second argument that the observed association is spurious involves a phenomenon known as “depletion of susceptibles.” Depletion of susceptibles occurs when the risk of an outcome appears to decline over time because those at highest risk for the event experience it early, leaving fewer high-risk individuals remaining in the population at later time periods. According to this argument, because desogestrel and gestodene were introduced into the market more recently than levonorgestrel, any given group of desogestrel and gestodene users is likely to contain a higher proportion of new starters of OCs than any given group of levonorgestrel users, and thus to contain a higher proportion of individuals with an elevated risk for VTE, because the “susceptibles” have not yet been depleted. Therefore, according to this argument, the observed associations may have resulted from the comparison of new users of desogestrel and gestodene with longer-term users of levonorgestrel. Thus, the “depletion of susceptibles” concern can be re-stated as failure to adequately account for duration of oral contraception use.

We set out to assemble all of the available data that assess the relative risk of VTE from desogestrel and gestodene versus levonorgestrel, to perform a quantitative synthesis, and to explore explanations for any variability in study results. In addition, we wished to characterize the degree of confounding that could have produced the observed association if, in truth, there were no cause-effect relationship. This would permit future discussion to focus on the plausibility of a given degree of confounding. We therefore performed a meta-analysis and formal sensitivity analysis of studies that examined the relative risk of VTE for OCs containing desogestrel and gestodene versus levonorgestrel.

2. Materials and methods

2.1. Meta-analysis

2.1.1. Identification and abstraction of data

In accordance with a written protocol, we performed a computer literature search in March 2000 using the search

strategy listed in the Appendix. All citations identified by this search (including the abstract, where available electronically) were reviewed by two reviewers, and the article was obtained if either reviewer thought that the article might meet the inclusion criterion or might contain references to papers meeting the inclusion criterion. We also examined the reference lists of retrieved articles.

Articles were included if they presented a relative risk estimate (or data sufficient to calculate a relative risk estimate) for deep vein thrombosis and/or pulmonary embolism for OCs containing gestodene or desogestrel plus EE at a dose of <50 mcg versus OCs containing levonorgestrel or other progestins plus EE at a dose of <50 mcg. We did not exclude studies on the basis of language or publication status (e.g. full article, abstract, manuscript, letter, etc.). We also sent an initial list of articles meeting the inclusion criterion to both the first author and apparent senior author of identified articles, to the US offices of major OC manufacturers, and to the US Food and Drug Administration, requesting that they identify any published or unpublished literature that was missed by our search.

Articles meeting the inclusion criterion were abstracted independently by two reviewers, who recorded the relevant relative risks, confidence intervals, and contingency table counts. The results of the two reviews were compared electronically, with discrepancies resolved by referring to the source article. We decided a priori not to calculate formal quality scores, but rather to examine features of studies as determinants of study results.

2.1.2. Calculation of summary relative risk estimates and evaluation of heterogeneity

When the original article did not report the relative risk of interest but did report figures that permitted their calculation, we performed these calculations. We computed 95% CIs for these derived relative risks, using the method of Greenland and Longnecker [9] when necessary to estimate the relevant covariance terms. If multiple relative risks were available for a given study or population, we included the best adjusted, most comprehensive result. When the best adjusted was not also the most comprehensive result, we gave preference to the best adjusted result and performed a secondary analysis by using any alternative value.

We used a random effects model to calculate summary estimates of the relative risk and performed a secondary analysis by using a fixed effects model [10]. All confidence intervals reported are 95%. We also performed a statistical test of the relationship between study size and relative risk to assess the possibility of publication bias [11]. In addition, we performed a statistical test of heterogeneity [12] and evaluated study-specific factors as sources of heterogeneity by examining estimates for different levels of those factors. For example, to examine the effect of accounting for duration of therapy, we examined results that accounted for and did not account for duration of exposure in studies in which

both estimates were available. All meta-analytic summaries were calculated by using STATA version 6.0 (STATA Corporation, College Station, Texas). In particular, we used the “meta” program (sbe 16.2) and the “metabias” program (sbe 19.1).

2.2. Sensitivity analysis

To examine the sensitivity of the summary effect estimate to different degrees of uncontrolled confounding, we performed a sensitivity analysis by using the method of Greenland [13], which relies on a 2×2 contingency table for the association being examined. To produce this table, we undertook a three-step process. First, we abstracted, wherever possible, the 2×2 table from each study. Second, we summed each quadrant of the 2×2 tables across studies to produce a single, unadjusted 2×2 table. However, such a table would not be expected to result in the summary odds ratio from the meta-analysis. Therefore, using the method of Greenland and Longnecker [9], we next held constant the resulting row and column totals of cases, controls, exposed, and unexposed (i.e. the margins) and adjusted the 2×2 table to reflect the summary odds ratio from the meta-analysis. We then used this imputed 2×2 table as the “observed” table that served as the basis of the sensitivity analysis.

We then calculated [13] what the true odds ratio and 95% CI would be under various scenarios concerning a single, hypothetical, unmeasured dichotomous confounding factor, or multiple such factors acting in concert to produce a joint effect of a given magnitude. In particular, we posited scenarios in which the prevalence of an unmeasured confounder in women taking levonorgestrel ranged from 5% to 40%, and was 1.5-, 2-, or 3-times more common in women receiving desogestrel or gestodene and in which the unmeasured confounder increased the risk of VTE by a factor of 2, 3, 4, 5, or 10. Because most published discussions have focused on whether unmeasured confounders have artificially elevated the observed associations, our sensitivity analysis considered only unmeasured confounding that would have resulted in an overestimate of the true odds ratio. Of course, confounding in the opposite direction could also have occurred.

3. Results

3.1. Meta-analysis

The computer literature search produced a total of 2609 references, and the manual methods produced an additional 36 references, for a total of 2645 citations screened. From these, we identified a total of 11 studies of different populations that met the inclusion criterion. Two additional studies meeting the inclusion criterion and published after our initial literature review [14,15] were also included (Table

1). One of these studies [14] supplanted the originally selected study [45] of the General Practice Research Database, a population that served as the basis for a number of potentially eligible articles. We chose the most recent eligible publication [14] because it included the most comprehensive time period of any available study. However, this choice had little impact on the summary relative risk (data not shown). Several articles [52–54] examined the risk of VTE from third generation OCs versus all other OCs, but were not included because they did not allow a comparison among products with <50 mcg EE. All studies meeting the inclusion criterion used an observational design.

Based on the 12 studies identified, the random effects summary relative risk for the effect of desogestrel or gestodene versus levonorgestrel was 1.7 (1.3–2.1; Table 1; Fig. 1). This summary estimate varied little based on the choice of available effect measures from a given population (data not shown). The fixed effects relative risk was very similar: 1.6 (1.4–1.9). A statistical test did not suggest the presence of publication bias ($p = 0.8$) [11]. The statistical test for heterogeneity resulted in a p value of 0.09, which we considered suggestive of differences among study results, given the limited statistical power of such tests [55,56]. Stratifying the results by study design, the cohort and nested case-control studies had a summary relative risk of 1.6 (1.0–2.5), while the non-nested case-control studies had a summary relative risk of 1.7 (1.3–2.2).

Four studies presented data allowing us to examine the impact of controlling for duration of contraceptive use within that study (Table 2). In those four studies, accounting for the effect of duration had a modest effect on the relative risk, reducing it from 2.1 (1.5–2.9) to 1.8 (1.2–2.8).

Three studies presented relative risks for less than 1 year of use in new users of OCs (Table 3). In these studies, there was a consistently elevated relative risk in the first year of use, with a summary odds ratio of 2.7 (1.4–5.4). In new users, there was also an increased risk in second and later years of use, with a summary odds ratio of 2.8 (1.0–7.4).

In most studies, the numerator for the relative risk of interest included two desogestrel formulations (desogestrel 150 mcg with EE 20 mcg and desogestrel 150 mcg with EE 30 mcg) and one gestodene formulation (gestodene 75 mcg with EE 30 mcg). In five studies [14,19,31,35,45], a separate estimate was available for each desogestrel formulation. In these five studies, the summary relative risks for the two desogestrel formulations were similar: 2.1 (1.2–3.6) and 2.2 (1.5–3.3) for 20 and 30 mcg of EE, respectively. Eight studies [14,17,19,21,31,35,45,47] presented data separately for desogestrel and gestodene. In these studies, the summary relative risks for desogestrel was 2.1 (1.6–2.8); for gestodene it was 1.8 (1.4–2.3), indicating that considering these two agents together as a group is reasonable on purely empirical grounds.

Table 1
 Characteristics of studies examining the relative risk of VTE from desogestrel and gestodene versus levonorgestrel with <50 mcg of ethinyl estradiol

Study (Reference number)	Relative risk estimate (95% CI)	Design	Factors adjusted for or found not to be confounders	Comments	Exposed cases	Unexposed cases	Exposed controls	Unexposed controls
AAH Meditel [16–18]	1.6 (0.6–4.2)	Cohort	Age by year		Not available	Not available	Not available	Not available
Amsterdam [19]	3.0 (1.2–7.6)	Case-control	Age by year, family history, calendar time, center		33	26	34	42
Denmark [20–24]	1.4 (0.8–2.3)	Case-control	Age by year, age at 1 st birth, duration, body mass index, education, family history, hypertension during pregnancy, smoking, diabetes		117	27	118	50
German MediPlus [25]	0.8 (0.4–1.6)	Nested case-control	Age by year	Definitions of 2 nd and 3 rd generation not provided.	15	27	64	89
GPRD-Boston Collaborative Drug Surveillance Program [14, 26,27]	2.3 (1.3–3.9)	Nested case-control	Age by year, index date, medical practice, body mass index, smoking, duration of use of OCs switching		64	42	278	291
Leiden Thrombophilia Study [28–30]	2.2 (0.9–5.4)	Case-control	Age by year, family history of venous thrombosis, factor V Leiden mutation	Gestodene not included in study. Estimate for triphasic levonorgestrel not included in reference group because it is grouped with norethisterone.	37	20	15	18
New Zealand [15]	2.9 (0.5–16.0)	Case-control	Age by year, weight, medical practice	Includes only fatal cases.	12	3	15	8
PHARMO [31, 32]	4.3 (1.8–10.7)	Cohort	Age by year, duration (<1y, ≥1y)	Includes only new users	Not available	Not available	Not available	Not available
Planned Parenthood [33]	1.0 (0.4–2.5)	Cohort	None	Cases ascertained by review of records maintained by the Planned Parenthood's risk management department.				
Transnational [34–43]	1.4 (1.0–1.9)	Case-control	Age by year, study center, body mass index, smoking, alcohol use, duration of OC use before the current exposure, duration of OC use during the current exposure	We used results from UK and Germany rather than "all country" results because the UK and Germany results were more fully adjusted. We used the logistic regression model adjusting for duration of past use and duration of current episode; because no CI was reported, we used the standard error from the same model as above, but not adjusted for duration of current episode.	137	115	264	354
UK MediPlus [44–46]	1.2 (0.7–2.1)	Nested case-control	Age by year, body mass index, asthma, smoking, blood pressure, number of prescription drugs		53	32	157	132
WHO [47–51]	2.3 (1.4–3.8)	Case-control	Duration (≤1, >1 y), body mass index, age in 5-year bands, center	Levonorgestrel group contained 1 case and 2 controls exposed to norgestimate 250&EE30. We used the results stratified on duration of use to calculate an average relative risk estimate across duration categories (≤1, >1 y).	71	137	56	203
Summary effect measure across studies	1.7 (1.3–2.1) (p-value for heterogeneity = 0.09)							

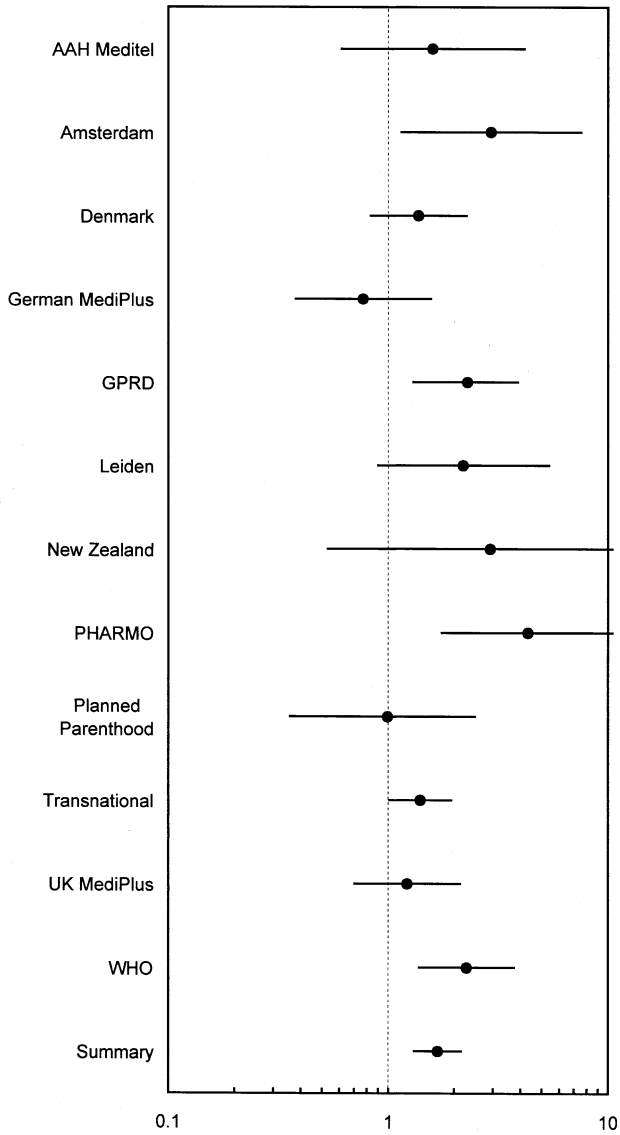


Fig. 1. Relative risk and 95% CIs for the relative risk of venous thromboembolism in users of oral contraceptives containing desogestrel or gestodene versus levonorgestrel.

3.2. Sensitivity analysis

Among the 12 studies, 2 × 2 tables were unavailable for three studies [17,32,33] because they were cohort studies with person-time in the denominator. Summing the cell counts for the other nine studies (Table 1) resulted in 539 exposed cases, 429 unexposed cases, 1001 exposed controls, and 1187 unexposed controls. Holding constant the margin totals of cases (n = 968), controls (n = 2188), exposed (n = 1540), and unexposed (n = 1616), and adjusting the 2 × 2 table to reflect the summary odds ratio of 1.7, produced an imputed table of 559 exposed cases, 409 unexposed cases, 981 exposed controls, and 1207 unexposed controls.

This imputed table was used as the basis for the sensitivity analysis, which examined odds ratios and 95% CIs in

Table 2

Relative risk estimates for VTE in users of OCs containing desogestrel or gestodene versus levonorgestrel in studies in which estimates accounting for and not accounting for the effect of duration were available

Study	Relative risk estimate (95% CI) not accounting for differences in duration of therapy	Relative risk estimate (95% CI) accounting for differences in duration of therapy
Denmark	1.6 (1.0–2.7)	1.4 (0.8–2.3)
PHARMO	4.2 (1.7–10.2)	4.3 (1.8–10.7)
Transnational	1.8 (1.3–2.5)	1.4 (1.0–1.9)
WHO	2.7 (1.6–4.6)	2.3 (1.4–3.8)
Summary	2.1 (1.5–2.9)	1.8 (1.2–2.8)
	(p-value for heterogeneity = 0.17)	(p-value for heterogeneity = 0.06)

a number of scenarios in which we varied the prevalence of an unmeasured confounding factor among women using the two categories of OCs, as well as the the magnitude of association between this unmeasured confounder and the occurrence of VTE (Table 4). For example, in the scenario in which an unmeasured factor tripled the risk of VTE and was present in 20% of women exposed to levonorgestrel and in 40% of women exposed to desogestrel or gestodene, the true relative risk accounting for this confounder would be 1.3 (1.1–1.5), rather than the observed relative risk of 1.7. In general, an association remained in scenarios in which the unmeasured confounding factor doubled the risk of VTE. In scenarios in which the factor increased the VTE risk 10-fold, the association generally abated unless the *relative* prevalence of the factor differed by 50% or less between study groups. For scenarios in which the factor increased the risk of VTE by a factor of 3–5, the presence of a significant association varied according to the prevalences in the study groups.

4. Discussion

The summary relative risk of VTE associated with use of desogestrel and gestodene versus levonorgestrel was 1.7

Table 3

Relative risk estimates for VTE for OCs containing desogestrel or gestodene versus levonorgestrel in studies in which estimates for early and late use in first-time users were available

Study	Relative risk estimate (95% CI) for <1 year use in first-time users	Relative risk estimate (95% CI) for >1 year use in first-time users
Netherlands	3.3 (1.2–8.9)	8.1 (1.0–63.6)
Transnational	2.2 (0.7–7.3)	1.5 (0.7–3.2)
WHO	2.4 (0.5–11.3)	4.4 (1.1–17.2)
Summary	2.7 (1.4–5.4)	2.8 (1.0–7.4)
	(p-value for heterogeneity = 0.86)	(p-value for heterogeneity = 0.18)

Table 4

Odds ratios and 95% CIs for the association between VTE and OCs containing desogestrel or gestodene versus those containing levonorgestrel, assuming 559 exposed cases, 409 unexposed cases, 981 exposed noncases, and 1207 unexposed noncases, for a measured odds ratio of 1.7 (1.4–2.0), and varying assumptions about the prevalence of an unmeasured confounder and the odds ratio for the association between the unmeasured confounder and the occurrence of VTE

Prevalence of confounder in women receiving levonorgestrel (%)	Prevalence of confounder in women receiving desogestrel or gestodene (%)	True odds ratio (95% CI) if the odds ratio for the association between the confounder and VTE = 2	True odds ratio (95% CI) if the odds ratio for the association between the confounder and VTE = 3	True odds ratio (95% CI) if the odds ratio for the association between the confounder and VTE = 4	True odds ratio (95% CI) if the odds ratio for the association between the confounder and VTE = 5	True odds ratio (95% CI) if the odds ratio for the association between the confounder and VTE = 10
5	7.5	1.6 (1.4–1.9)	1.6 (1.4–1.9)	1.6 (1.3–1.8)	1.5 (1.3–1.8)	1.5 (1.2–1.7)
5	10	1.6 (1.4–1.9)	1.5 (1.3–1.8)	1.5 (1.3–1.7)	1.4 (1.2–1.7)	1.3 (1.1–1.5)
5	15	1.5 (1.3–1.8)	1.4 (1.2–1.7)	1.3 (1.1–1.6)	1.3 (1.1–1.5)	1.0 (0.9–1.2)
10	15	1.6 (1.4–1.9)	1.5 (1.3–1.8)	1.5 (1.3–1.8)	1.5 (1.2–1.7)	1.4 (1.1–1.6)
10	20	1.5 (1.3–1.8)	1.4 (1.2–1.7)	1.4 (1.2–1.6)	1.3 (1.1–1.5)	1.1 (1.0–1.4)
10	30	1.4 (1.2–1.7)	1.3 (1.1–1.5)	1.1 (1.0–1.4)	1.1 (0.9–1.3)	0.9 (0.7–1.0)
20	30	1.5 (1.3–1.8)	1.5 (1.3–1.7)	1.4 (1.2–1.7)	1.4 (1.2–1.6)	1.3 (1.1–1.5)
20	40	1.4 (1.2–1.7)	1.3 (1.1–1.5)	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.0 (0.9–1.2)
20	60	1.3 (1.1–1.5)	1.1 (0.9–1.3)	1.0 (0.8–1.1)	0.9 (0.7–1.1)	0.7 (0.6–0.9)
30	45	1.5 (1.3–1.8)	1.4 (1.2–1.7)	1.4 (1.2–1.6)	1.3 (1.1–1.6)	1.2 (1.0–1.5)
30	60	1.4 (1.2–1.6)	1.2 (1.0–1.4)	1.1 (1.0–1.3)	1.1 (0.9–1.3)	1.0 (0.8–1.2)
30	90	1.1 (1.0–1.4)	1.0 (0.8–1.2)	0.9 (0.7–1.0)	0.8 (0.7–1.0)	0.7 (0.6–0.8)
40	60	1.5 (1.3–1.7)	1.4 (1.2–1.6)	1.3 (1.1–1.5)	1.3 (1.1–1.5)	1.2 (1.0–1.4)
40	80	1.3 (1.1–1.5)	1.2 (1.0–1.4)	1.1 (0.9–1.3)	1.0 (0.9–1.2)	0.9 (0.8–1.1)

Boldface type indicates $p < 0.05$.

(1.3–2.1) from the available studies, all of which are observational. The direction of the association was reasonably consistent across studies and across study designs. Although consistency enhances the plausibility of an association, it also remains possible that the same sources of bias, or even different sources of bias acting in the same direction, could have produced such consistency. The summary estimate depended little on the choice of a random versus fixed effects meta-analytic model, choice of estimates from individual studies, or grouping versus separating the two desogestrel products together with gestodene.

The available data suggest that confounding by duration of exposure (and therefore, bias caused by depletion of susceptibles) does not account for the observed association. This is because an association was evident in analyses that accounted for duration of exposure and because depletion of susceptibles could not have produced the association that was present in the first year of use among new users.

Well-known factors that may influence the risk of VTE had been removed as sources of potential confounding in the major studies through exclusion, matching, or statistical adjustment (Table 1). However, unmeasured confounding is always a concern in observational studies and consequently in meta-analyses of their results. It is for this reason that we performed a formal sensitivity analysis to quantify the degree of unmeasured confounding that could have produced the observed association if there were no cause-effect relationship.

In the sensitivity analysis, the association abated in many, but not all, examined scenarios in which the unmeasured

factor increased the risk of VTE by a factor of 3–5 and in nearly all in which the factor increased the risk of VTE 10-fold. Although no firm standards exist, we believe that this result indicates sensitivity to modest confounding. This sensitivity is not surprising given that the summary relative risk was 1.7, which is conventionally considered a weak association. Furthermore, this sensitivity analysis only examined the effect of a single unmeasured dichotomous confounding factor or multiple confounders whose joint effect was of the same magnitude. Naturally, the results would be even more sensitive to the presence of additional unmeasured confounding.

Sensitivity to a modest degree of confounding is not, however, evidence that such confounding actually occurred. Thus, although one need not invoke strong unmeasured confounding to argue that the association is spurious, the existence of *any* degree of unmeasured confounding remains open to discussion. For example, although there are known genetic factors that increase the risk of VTE by a factor of 10 or more [5], whether exposure to different OC formulations varies according to correlates of these factors remains unknown. Other examples of possible risk factors for VTE are family history, with a relative risk of about 3 [28]; elevated body mass index, with a relative risk of about 2–5 [45,48]; and history of varicose veins, with a relative risk of about 4 [48]. Had the summary relative risk been insensitive to a high degree of confounding (e.g., a confounder that increased the risk of VTE 10-fold), then it might well have been reasonable to dismiss that degree of confounding as implausible in this setting. It is more diffi-

cult, however, to dismiss the possibility of a modest degree of confounding in observational data such as these. Therefore, it seems doubtful that observational studies will be able to unequivocally discern whether the observed weak association is causal or spurious. The conduct of a randomized trial large enough to definitively answer this question would be a challenging endeavor.

If the observed relative risk of 1.7 represents a true cause-effect relationship, then the incremental risk of VTE in young women is numerically small, from about 15 per 100,000 in women per year for levonorgestrel [57] to about 26 per 100,000 per year for desogestrel or gestodene. However, about 2% of individuals in this population experiencing VTE will die from it [58], and about 20% will experience a post-thrombotic syndrome [58], which can cause long-term disability [59].

In conclusion, results of observational studies indicate that desogestrel and gestodene appear to increase the risk of VTE by approximately 1.7-fold versus levonorgestrel. Although this association does not appear to be caused by depletion of susceptibles, a modest degree of unmeasured confounding could have produced such an association. Because of this sensitivity to unmeasured confounding, it is doubtful that this causal question can be answered definitively by using observational data. In the absence of a definitive answer, this apparent increased risk, together with uncertainty, small magnitude, and its important individual consequences should be considered when selecting an OC for a given woman.

Appendix: Bibliographic Search Strategy

Medline

1. exp contraceptive agents, female/
2. exp norpregnanes/
3. exp desogestrel/[No MESH terms exist for gestodene]
4. "contracep\$.mp
5. "norpregnene\$.mp
6. "desogestrel\$.mp
7. "gestodene\$.mp
8. "norgestimate\$.mp
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp thrombosis/
11. exp pulmonary embolism/
12. "thromb\$.mp
13. "embol\$.mp
14. 10 or 11 or 12 or 13
15. 9 and 14
16. limit 15 to human
17. limit 16 to yr = 1975–2000 [first of 3rd generation agents was registered as a potential drug in 1975]

Note that "exp" refers to explode, meaning to identify articles including that term, even if the article is not focused on that term. This is in contrast to "focus." The suffix "\$" is

the appropriate wildcard in these databases. The suffix ".mp" indicates that the term will be searched for as free text in the title, abstract (where available), and MeSH terms (where available). Thus, this strategy makes maximal use of MeSH indexing, although it does not rely on correct or complete indexing.

Healthstar

Same strategy as for MedLine, with the additional qualifier "not included in Medline."

Cumulative index to nursing and allied health (CINAHL)

1. exp contraceptives, oral/
2. "contracep\$.mp
3. "norpregnene\$.mp
4. "desogestrel\$.mp
5. "gestodene\$.mp
6. "norgestimate\$.mp
7. 1 or 2 or 3 or 4 or 5 or 6455555
8. exp thrombosis/
9. exp pulmonary embolism/
10. "thromb\$.mp
11. "embol\$.mp
12. 8 or 9 or 10 or 11 13.7 and 12

[CINAHL goes back only as far as 1982, so no date restriction is needed.]

Science citation index (SCI)

(contracep or norpregnene or desogestrel or gestodene or norgestimate) and (thromb or embol)

References

- [1] WHO Scientific Group on Cardiovascular Disease, and Steroid Hormone Use. Cardiovascular disease and steroid hormone contraception. Geneva: World Health Organization, 1997.
- [2] Kuhl H, Jung-Hoffmann C, Wiegatz I. Gestodene-containing contraceptives. *Clin Obstetr Gynecol* 1995;38:829–40.
- [3] Lammers P, Blumenthal PD, Huggins GR. Developments in contraception: a comprehensive review of Desogen (desogestrel and ethinyl estradiol). *Contraception* 1998;57:1S–27S.
- [4] Walker AM. Newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1998;57:169–81.
- [5] Farley TM, Meirik O, Collins J. Cardiovascular disease and combined oral contraceptives: reviewing the evidence and balancing the risks. *Hum Reprod Update* 1999;5:721–35.
- [6] Walker AM. Gestodene, desogestrel, and venous thromboembolism: a little risk after a long look. *J Clin Endocrinol Metab* 1999;84:1825–8.
- [7] Lewis MA. The epidemiology of oral contraceptive use: a critical review of the studies on oral contraceptives and the health of young women. *Am J Obstet Gynecol* 1998;179:1086–97.
- [8] Spitzer WO. Bias versus causality: interpreting recent evidence of oral contraceptive studies. *Am J Obstet Gynecol* 1998;179:S43–S50.

- [9] Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992;135:1301–9.
- [10] Berlin JA. The use of meta-analysis in pharmacoepidemiology. In: Strom BL, editor. *Pharmacoepidemiology*, 3rd ed. Chichester: John Wiley & Sons, 2000. p. 633–60.
- [11] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
- [12] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
- [13] Greenland S. Basic methods for sensitivity analysis of biases. *Int J Epidemiol* 1996;25:1107–16.
- [14] Jick H, Kay JA, Vasilakis-Scaramozza C, Jick SS. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *BMJ* 2000;321:1190–5.
- [15] Parkin L, Skegg DC, Wilson M, Herbison GP, Paul C. Oral contraceptives and fatal pulmonary embolism (letter). *Lancet* 2000;355:2133–4.
- [16] Farmer RD, Preston TD. The risk of venous thromboembolism associated with low oestrogen oral contraceptives. *J Obstet Gynaecol* 1995;15:195–200.
- [17] Farmer R. Safety of modern oral contraceptives (letter). *Lancet* 1996;347:259.
- [18] Farmer RD, Lawrenson R. Utilization patterns of oral contraceptives in UK general practice. *Contraception* 1996;53:211–5.
- [19] Bloemenkamp KW, Rosendaal FR, Buller HR, Helmerhorst FM, Colly LP, Vandenbroucke JP. Risk of venous thrombosis with use of current low-dose oral contraceptives is not explained by diagnostic suspicion and referral bias. *Arch Intern Med* 1999;159:65–70.
- [20] Lidegaard O. The influence of thrombotic risk factors when oral contraceptives are prescribed. A control-only study. *Acta Obstet Gynecol Scand* 1997;76:252–60.
- [21] Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism. A case-control study. *Contraception* 1998;57:291–301.
- [22] Lidegaard O. Thrombotic diseases in young women and the influence of oral contraceptives. *Am J Obstet Gynecol* 1998;179:S62–S67.
- [23] Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism. *Contraception* 1998;58:199–200.
- [24] Lidegaard O. Smoking and use of oral contraceptives: impact on thrombotic diseases. *Am J Obstet Gynecol* 1999;180:S357–S363.
- [25] Farmer RD, Todd JC, Lewis MA, MacRae KD, Williams TJ. The risks of venous thromboembolic disease among German women using oral contraceptives: a database study. *Contraception* 1998;57:67–70.
- [26] Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995;346:1589–93.
- [27] Vasilakis C, Jick SS, Jick H. The risk of venous thromboembolism in users of postcoital contraceptive pills. *Contraception* 1999;59:79–83.
- [28] Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Buller HR, Vandenbroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. *Lancet* 1995;346:1593–6.
- [29] Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Venous thromboembolism and oral contraceptives (letter). *Lancet* 1999;354:1469–70.
- [30] Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Higher risk of venous thrombosis during early use of oral contraceptives in women with inherited clotting defects. *Arch Intern Med* 2000;160:49–52.
- [31] Herings RM, Urquhart J, Leufkens HG. Venous thromboembolism among new users of different oral contraceptives (letter). *Lancet* 1999;354:127–8.
- [32] Herings RM, Urquhart J, Leufkens HG. Venous thromboembolism and oral contraceptives (letter). *Lancet* 1999;354:1469–70.
- [33] Burnhill MS. The use of a large-scale surveillance system in Planned Parenthood Federation of America clinics to monitor cardiovascular events in users of combination oral contraceptives. *Int J Fertil Womens Med* 1999;44:19–30.
- [34] Lewis MA, Assmann A, Heinemann L, Spitzer WO. Interim review of the transnational case-control study of oral contraceptives and health. Approved protocol revisions through September 1995. *Pharmacoepidemiol Drug Safety* 1996;5:43–51.
- [35] Lewis MA, Heinemann LA, MacRae KD, Bruppacher R, Spitzer WO. The increased risk of venous thromboembolism and the use of third generation progestagens: role of bias in observational research. The Transnational Research Group on Oral Contraceptives and the Health of Young Women. *Contraception* 1996;54:5–13.
- [36] Spitzer WO, Lewis MA, Heinemann LA, Thorogood M, MacRae KD. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. Transnational Research Group on Oral Contraceptives and the Health of Young Women. *BMJ* 1996;312:83–8.
- [37] Suissa S, Blais L, Spitzer WO, Cusson J, Lewis M, Heinemann L. First-time use of newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1997;56:141–6.
- [38] Lewis MA, Spitzer WO. The role of bias in observational studies of oral contraceptives (letter). *Contraception* 1997;55:189–94.
- [39] Heinemann LA, Assmann A, DoMinh T, Garbe E. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. *Europ J Contracept Reprod Health Care* 1999;4:67–73.
- [40] Lewis MA, MacRae KD, Kuhl-Habich D, Heinemann LA. Venous thromboembolism and oral contraceptives (letter). *Lancet* 1999;354:1470.
- [41] Lewis MA. The Transnational Study on Oral Contraceptives and the Health of Young Women. Methods, results, new analyses and the healthy user effect. *Hum Reprod Update* 1999;5:707–20.
- [42] Lewis MA, MacRae KD, Kuhl-Habich D, Bruppacher R, Heinemann LA, Spitzer WO. The differential risk of oral contraceptives: the impact of full exposure history. *Hum Reprod* 1999;14:1493–9.
- [43] Lewis MA, MacRae KD, Kuhl-Habich D, Heinemann LAJ. Risk of venous thromboembolism in first users of oral contraceptive exposures with different times on market (abstract). *Pharmacoepidemiol Drug Safety* 2000;9(Suppl 1):S148.
- [44] Farmer RD, Lawrenson RA, Thompson CR, Kennedy JG, Hambleton IR. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. *Lancet* 1997;349:83–8.
- [45] Farmer RD, Lawrenson RA, Todd JC, Williams TJ, MacRae K. Oral contraceptives and venous thromboembolic disease. Analyses of the UK General Practice Research Database and the UK Mediplus database. *Hum Reprod Update* 1999;5:688–706.
- [46] Todd J, Lawrenson R, Farmer RD, Williams TJ, Leydon GM. Venous thromboembolic disease and combined oral contraceptives: a re-analysis of the MediPlus database. *Hum Reprod* 1999;14:1500–5.
- [47] Farley TMM, Meirik O, Chang CL, Marmot MG, Poulter NR. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet* 1995;346:1582–8.
- [48] Poulter NR, Farley TMM, Chang CL, Marmot MG, Meirik O. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet* 1995;346:1575–82.
- [49] Farley TM, Meirik O, Poulter NR, Chang CL, Marmot MG. Oral contraceptives and thrombotic diseases: impact of new epidemiological studies (letter). *Contraception* 1996;54:193–8.

- [50] Farley TM, Meirik O, Chang CL, Poulter NR. Combined oral contraceptives, smoking, and cardiovascular risk. *J Epidemiol Community Health* 1998;52:775–85.
- [51] Poulter NR, Farley TM, Chang CL, Marmot MG, Meirik O. Safety of combined oral contraceptive pills (letter). *Lancet* 1996;347:547.
- [52] Andersen BS, Olsen J, Nielsen GL, et al. Third generation oral contraceptives and heritable thrombophilia as risk factors of non-fatal venous thromboembolism. *Thromb Haemost* 1998;79:28–31.
- [53] Bennet L, Odeberg H. Resistance to activated protein C, highly prevalent amongst users of oral contraceptives with venous thromboembolism. *J Intern Med* 1998;244:27–32.
- [54] Martinelli I, Taioli E, Bucciarelli P, Akhavan S, Mannucci PM. Interaction between the G20210A mutation of the prothrombin gene and oral contraceptive use in deep vein thrombosis. *Arterioscler Thromb Vasc Biol* 1999;19:700–3.
- [55] Fleiss JL. Analysis of data from multiclinic trials. *Control Clin Trials* 1986;7:267–75.
- [56] Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. *Stat Med* 1998;17:841–56.
- [57] Mayor S. Department of health changes advice on third generation pills. *BMJ* 1999;318:1026.
- [58] Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999;353:1167–73.
- [59] McNally MA, McAlinden MG, O'Connell BM, Mollan RA. Post-phlebotic syndrome after hip arthroplasty. 43 patients followed at least 5 years. *Acta Orthop Scand* 1994;65:595–8.