among users of third-generation OCs tend to be within normal ranges, the observation of APC-resistance may explain why this property does not benefit the user population. Fourth, the observation of one isolated event might not be sufficient and may produce a fallacy similar to the one regarding the relation of beta blockers and cholesterol metabolism. Fifth, we would expect to find a profound difference in VTE distribution when comparing users of second-generation with third-generation OCs. A stratification of the cases in the Transnational Study shows that this is not so. But, finally, the first results of an ongoing population-based study conducted on 822 Bavarian women in whom ProC global and APC COA tests were done show the expected differences in APC-resistance related to factor V Leiden mutation, but no differences related to OC use (Schramm W, Heinemann LAJ, unpublished).

The most important aspect to consider, however, is the impact on the population. Your commentators lead us astray when they divide the world of women into winners and losers. On a population basis, the results for VTE are unlikely to produce a difference, especially since third-generation OCs are the first without excess risk of myocardial infarction. Unfortunately, the third-generation-pill controversy is still ongoing.

*Michael A Lewis, Lothar A J Heinemann
*EPES Epidemology, Pharmacoepidemiology and Systems Research, Transnational Study on Oran Contraceptives and the Health of Young Women, D-12165 Berlin, Germany and Centre for Epidemiology and Health Research (ZEG) Berlin, Zepernick

1 Vandenbroucke JP, Rosendaal FR End of the line for "third-generation-pill" controversy? *Lancet* 1997, **349:** 1113–14
2 Rosing J, Tans G, Nicolaes GAF, et al Oral contraceptives and venous thrombosis different sensitivities to activated protein C in women using second- and third generation oral contraceptives *Br J Haematol* 1997, **97:** 233–38
3 Lewis MA, Heinemann LAJ, 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 *Contraception* 1996, **54:** 5–13
4 Kuhl H, Jung-Hoffman C, Heidt F Alterations of the serum levels of Gestodene and SHBG during 12 cycles of treatment with 30 micrograms ethinylestradiol and 75 micrograms gestodene *Contraception* 1988, **38:** 477–86

SIR—Vandenbroucke and Rosendaal state that Rosing and colleagues'[1] report "proves" that there is a thrombogenic difference between second-generation and third-generation OCs. However, since the study was not randomised, causality cannot be inferred. The study, while showing an interesting effect on APC, does not preclude the possibility that women using third-generation pills were in some way different from those using second-generation pills.

It should not be forgotten that third-generation pills may have arterial disease benefits. The final results of the Transnational Study showed a statistically significant reduction in risk of myocardial infarction (MI) in third-generation compared with second-generation pill users (RR 0·3, 95% CI 0·1–0·9), which is in line with the study by Jick et al,[2] although the latter results were not statistically significant. A risk-benefit modelling analysis done in the USA[3] has calculated that in women aged 35–44, the possible increase in the risk of venous thrombosis in third-generation pill uses would be more than offset by the benefit in a reduced incidence of MI. In addition, although more difficult to quantify, third-generation pills are generally perceived as better tolerated and with fewer nuisance side-effects such as acne and hirsutism. These benefits should not be ignored because of a possible slight increase (even if real) in a rare and very rarely fatal condition.

*Anne Szarewski, Barbara Hollingworth, Diana Mansour, Naomi Hampton, Martyn Walling
*Department of Mathematics, Statistics, and Epidemiology, Imperial Cancer Research Fund, London WC2A 3PX, UK Department of Obstetrics and Gynaecology, Luton and Dunstable Hospital, Luton, Community Gynaecology and Reproductive Health Care, Newcastle upon Tyne City NHS Trust, Reproductive Health and Community Gynaecology, Enfield Community Care NHS Trust, and Boston, Lincolnshire

1 Rosing J, Tans G, Nicolaes GAF, et al. Oral contraceptives and venous thrombosis different sensitivities to activated protein C in women using second and third generation oral contraceptives *Br J Haematol* 1997; **97:** 233–38
2 Jick H, Jick S, Myers MW, Vasilakis C Risk of acute myocardial infarction and low-dose combined oral contraceptives *Lancet* 1996, **347:** 627–28
3 Schwingl PJ, Shelton J Modeled estimates of myocardial infarction and venous thromboembolic disease in users of second and third generation oral contraceptives *Contraceptives* 1997, **55:** 125–29

## Authors' reply

SIR—Your correspondents seem not to doubt any more that there is some reality in the association between third-generation contraceptives and an increased risk of venous thrombosis. We are grateful for this important progress in comparison with previous rounds of discussion in *The Lancet*. The argument is now shifted to the true magnitude of the risk, the explanatory strength of the new coagulation findings, and the balance of risks and benefits.

The discussion about the magnitude of the risk still uses the "recency of introduction" argument. This has now been shown to be a matter of subgroup analysis.[1,2] That the haemostatic study to which we refer was not randomised is unimportant. The mere mentioning of an unqualified theoretical bias that has not been shown to affect the results serves little purpose. The philosopher Hume has stated that causal statements do not follow from observations, but from inference. It is extremely unlikely that general practitioners who prescribed third-generation and second-generation contraceptives selected the women so as to prescribe one brand to those with an unknown haemostatic abnormality. The relevance of the haemostatic test is shown in its correspondence with the level of risk due to the factor V Leiden mutation, and in the interaction with that mutation. The recent calculation of the balance of arterial benefits and venous risks[3] carried a specific warning that all calculations rest upon the assumption of a close to 70% decrease in risk of myocardial infarction with the use of third-generation contraceptives, as was found in the Transnational Study. By contrast, the WHO report (April 26, p 1202)[4] shows that very little risk remains, either with second-generation or third-generation contraceptives, after simple screening for arterial risk factors. Finally, Lidegaard and Milsom, in their earlier commentary (to which they refer), wrote that there was no difference in risk of cerebrovascular accidents between second-generation and third-generation contraceptives, which was later corroborated in an analysis from the WHO study.[5] This finding opens the possibility that views are also converging in this issue. With the uncertainties, we refrained from speculation about the arterial risk in our commentary. By contrast with your correspondents, we also refrained from specific recommendations to the authorities, but only mentioned that steps were necessary.

Several of your correspondents tell us that the tone and style of our commentary does not make a useful contribution to the debate. However, what else can one express, apart from deep amazement, when claims of "biases" are repeated long after it has been shown that they do not lead to any alteration of the estimates? In the recent exchange of views about silicone breast implants and autoimmune disease, *The Lancet* took the uncommon but highly interesting step of asking the contributors to state their possible "conflicts of interest"; perhaps this habit should be continued.

*Jan P Vandenbroucke, Frits R Rosendaal
Department of Clinical Epidemiology, Leiden University Hospital, PO Box 9600, 2300 RC Leiden, Netherlands

1 Weiss N. Bias in studies of venous thromboembolism in relation to the use of new formulations of oral contraceptives. *Contraception* 1997; **55:** 189–90.
2 Vandenbroucke JP, Bloemenkamp KWM, Helmerhorst FM, Rosendaal FR. Risk of oral contraceptives and recency of introduction. *Contraception* 1997; **55:** 191–92.
3 Schwingl PJ, Shelton J. Modeled estimates of myocardial infarction and venous thromboembolic disease in users of second and third generation oral contraceptives. *Contraception* 1997; **55:** 125–29.
4 WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Acute myocardial infarction and oral contraceptives: results of an international multicentre case-control study. *Lancet* 1997; **349:** 1202–09.
5 WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and oral contraceptives: results of an international multicentre case-control study. *Lancet* 1996; **348:** 498–504.

SIR—Vandenbroucke and Rosendaal[1] highlight the finding that third-generation oral contraceptives induce a resistance to activated protein C (APC, a natural anticoagulant defence mechanism), of about the same magnitude as the resistance induced by a mutation in coagulation factor V (factor V Leiden). This observation provides a neat explanation for the threefold increase in risk of DVT encountered with such oral contraceptives and for their interaction with the factor V Leiden mutation for DVT risk. In an epidemiological study of APC resistance, we have noted that this phenotype is associated not only with OC use and with factor V Leiden, but also with three other risk factors for DVT, the mechanisms of which have been hitherto unexplained: use of hormone replacement therapy (HRT),[2] obesity,[3] and high plasma coagulation factor VIII.[4]

In the third World Health Organisation MONICA survey, we measured APC resistance (original assay, Chromogenix, Stockholm, Sweden; with an ACL 300 Research Coagulometer, IL, Warrington, UK) in 460 men and 495 women aged 25–74 years, who were randomly sampled from general practice registers of the North Glasgow population. The table shows that increased age-standardised APC resistance (a lower APC ratio) was similarly associated with use of HRT among post-menopausal women aged 45–54 years,[2] use of OCs among women aged 25–34 years,[5] obesity (a body mass index of 30 kg/m² or more),[3] a factor VIII level of 150 IU/dL or more[4] (one-stage assay, ACL coagulometer), and with the factor V Leiden mutation.[1] The prevalence of factor V Leiden mutation was only 4% in this population, and exclusion of persons with this mutation did not affect the associations of APC resistance with the other four risk factors for DVT.

| | Yes | No | p |
|---|---|---|---|
| HRT use (post-menopausal F, 45–54 yr) | n=14 2·54 (2·31, 2·80) | n=47 2·92 (2·77, 3·07) | 0·016 |
| OC use (F, 25–34 yr) | n=24 2·57 (2·40, 2·75) | n=52 2·79 (2·67, 2·93) | 0·045 |
| BMI≥30 kg/m² (M+F, 25–74 yr) | n=150 2·69 (2·61, 2·78) | n=793 2·83 (2·79, 2·87) | 0·002 |
| Factor VIII ≥150 IU/dL (M+F, 25–74 yr) | n=395 2·68 (2·63, 2·73) | n=518 2·91 (2·87, 2·96) | 0·0001 |
| V Leiden carrier (M+F, 25–74 yr) | n=15 2·28 (2·07, 2·51) | n=696 2·81 (2·77, 2·85) | 0·0001 |

OC=oral contraceptive; BMI=body mass index, M=male; F=female. p values are for a difference in log (APC ratio) after age-adjustment; means and 95% CIs are back-transformed.

**Age-adjusted mean (95% CI) activated protein C (APC) ratios**

These findings accord with those of others[1,5] of an effect of oral contraceptives on APC resistance. They also suggest that APC resistance may be a common mechanism through which several recently recognised[2-4] risk factors for DVT (HRT use, obesity, high factor VIII) may operate, at least individually. Pregnancy might increase risk of DVT partly through a similar effect.[5] Further studies should examine (longitudinally as well as cross-sectionally) the effects of individual OC or HRT preparations on APC resistance and interactions with DVT risk; and whether such relations are interactive, in accordance with a postulated multiple-hit model for pathogenesis of DVT. Such studies are potentially clinically important for stratification of DVT risk in prescription of OCs or HRT, in pregnancy, and in obesity; as well as for elucidating the pathogenesis of DVT in these conditions.

*Gordon D O Lowe, Ann Rumley, Mark Woodward, Evan Reid
*University Department of Medicine, Royal Infirmary, Glasgow G31 2ER, UK; Department of Applied Statistics, University of Reading; and Department of Medical Genetics, Yorkhill Hospital, Glasgow

1 Vandenbroucke JP, Rosendaal FR. End of the line for "third-generation" pill controversy? *Lancet* 1997; **349:** 1113–14.
2 Vandenbroucke JP, Helmerhorst FM. Risk of venous thrombosis with hormone-replacement therapy. *Lancet* 1996; **348:** 972.
3 Goldhaber SZ, Savage DD, Garrison RJ, et al. Risk factors for pulmonary embolism: the Framingham Study. *Am J Med* 1983; **74:** 1023–28.
4 Koster T, Blann AD, Briet E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. *Lancet* 1995; **345:** 152–55.
5 Meinardi JR, Henkens CMA, Heringa MP, van der Meer J. Acquired APC resistance related to oral contraceptives and pregnancy and its possible implications for clinical practice. *Blood Coag Fibrinol* 1997; **8:** 152–54.

## Musculoskeletal side-effects of varicella

SIR—Burke and Chambers (Mar 22, p 818)[1] describe a recent increase in musculoskeletal complications of varicella requiring surgery caused by group-A β-haemolytic streptococcus. As mentioned in this commentary, the recent resurgence of invasive group-A streptococcal disease worldwide may be due to a change in the epidemiology of group-A streptococcus, with an increase in the proportion of strains with M types associated with greater virulence. Although it is likely that changes in bacterial virulence are an important factor, host factors may also have contributed to the changing epidemiology of group-A streptococcal disease. It has been suggested that changes in strain-specific population immunity with time are responsible for the emergence of new strains.[2]

Certain individuals are known to be at increased risk of invasive group-A streptococcal disease. Traditionally, this disease has been associated with the elderly and patients with debilitating illness. In addition, it has been suggested that there may be genetic predisposing factors, such as MHC class II type or T-cell receptor Vβ repertoire.[3] At a more practical level, there has also been increasing recognition of the possible link between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the development of invasive group-A streptococcal disease, including necrotising fasciitis. Stevens[4] has proposed a mechanism that could account for such an association. NSAIDs inhibit neutrophil function and augment cytokine production in vitro. In addition, NSAIDs may mask the cardinal signs of inflammation that may otherwise lead to early recognition and treatment of invasive disease.

At present, it is not possible to be certain if the link between the use of NSAIDs and invasive group-A streptococcal disease is causal. This association may simply reflect the greater use of NSAIDs in patients with severe disease. NSAIDs are increasingly being proposed as first-line antipyretic drugs in both adults and children.[5] In the light of the documented increase in invasive group-A streptococcal disease and the hypothetical link between the use of NSAIDs and this disease, it may be prudent to avoid the widespread use of NSAIDs as antipyretics in patients in whom the diagnosis is uncertain and particularly in those with varicella.