

Vessey M P & Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. *Brit. Med. J.* 2:199-205, 1968.

[Medical Research Council's Statistical Research Unit, University College Hospital Medical School, London, England]

Contraceptive histories were obtained from 58 young women admitted to hospital with venous thromboembolism without evident predisposing cause and from 116 matched controls. Current oral contraceptive use was estimated to increase the risk of hospitalisation for venous thromboembolism about ninefold. [The SCF[®] indicates that this paper has been cited in over 320 publications.]

Martin P. Vessey

University Department of Community
Medicine & General Practice
Radcliffe Infirmary
Oxford OX2 6HE
England

November 29, 1985

I joined the Medical Research Council (MRC) Statistical Research Unit in 1966, having already done some epidemiological research in the field of obstetrics and gynaecology. At that time, the MRC was concerned about the anecdotal evidence linking oral contraceptive (OC) use with thromboembolism. Richard Doll (director of the unit) and I proposed undertaking a controlled study of hospital patients. At the same time, Inman and I were involved in a national study of fatal thromboembolic disease,¹ and the Royal College of General Practitioners was at work on an investigation of patients with thromboembolism seen in general practice.²

I started the project on a pilot basis at University College Hospital and the Central Middlesex Hospital, looking through the case records of women with a discharge diagnosis of thromboembolism. It soon became apparent that many thromboembolic events occurred during pregnancy or the puerperium, after surgery or trauma, or during the course of a severe illness, circumstances under which any etiological role that oral contraceptives might have would be very hard to detect. Accordingly, we resolved to concentrate on thromboembolism occurring in the absence of a recognised

predisposing cause ("idiopathic" thromboembolism) and drew up appropriate criteria for the inclusion or exclusion of patients.

The final study protocol involved 19 hospitals, the use of hospital patients without thromboembolism as controls, and the conduct of detailed home interviews by Keena Jones with all patients after discharge home. Although idiopathic thromboembolism was uncommon, a very high proportion of episodes involving the venous system (26/58 or 45 percent) occurred in current OC users (but not in past users). Numbers of women with idiopathic cerebral thrombosis or acute myocardial infarction were really too few to investigate, but there was an indication of an association between current OC use and the former condition (OC users 5/9), but not the latter (OC users 0/13).

We recognised that a potential weakness of our results concerning venous thromboembolism was that bias in diagnosis might have occurred; that is, that the use of OCs might have led to the presentation and recognition of disease that would otherwise have been missed. We found, however, that current OC use was most frequent among those who had the most certain (and most severe) forms of disease (OC users 9/12), which made this explanation for our findings most unlikely.

Once we had worked out our methodology, there were no particular obstacles during the conduct of this research—doctors and patients alike were friendly and cooperative. It is to be hoped that the implementation of the Data Protection Act in Britain will not interfere with studies of a similar kind in the future.

Our paper has been frequently cited because, with the other two studies already mentioned,^{1,2} it was the first to provide clear evidence that thromboembolism is a hazard of oral contraceptive use. Many other studies have subsequently confirmed this finding.³ The paper (and an update based on larger numbers)⁴ is also methodologically interesting and is, I know, a favourite even now amongst teachers of epidemiology.

Reviews of recent studies include one of my own³ and one by Realini and Goldzieher.⁵ We have some preliminary plans to undertake a new study of venous thromboembolism in centres using modern methods of diagnosis of the disease.

Finally, my work on OCs and thromboembolism launched me on a research career that still occupies much of my time—the assessment of the efficacy, acceptability, and safety of fertility control methods.

1. Inman W H W & Vessey M P. Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. *Brit. Med. J.* 2:193-9, 1968. [See also: Inman W H W. Citation Classic. *Current Contents/Clinical Practice* 8(44):12, 3 November 1980.]
2. Royal College of General Practitioners. Oral contraceptive and thromboembolic disease. *J. Coll. Gen. Practit.* 13:267-79, 1967.
3. Vessey M P. Female hormones and vascular disease—an epidemiological overview. *Brit. J. Fam. Plan.* 6(Suppl.):1-12, 1980. (Cited 35 times.)
4. Vessey M P & Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. *Brit. Med. J.* 2:651-7, 1969. (Cited 325 times.)
5. Realini J P & Goldzieher J W. Oral contraceptives and cardiovascular disease: a critique of the epidemiological studies. *Amer. J. Obstet. Gynecol.* 152:729-98, 1985.