

This Week's Citation Classic

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. [Committee on Safety of Drugs, Queen Anne's Mansions, and Med. Res. Council, Stat. Res. Unit, Univ. Coll. Hosp. Med. Sen., London, England]

A study in which women who died from various types of thromboembolism in the United Kingdom during 1966 were practice-matched with healthy women revealed a significant excess of oral contraceptive use among those dying from cerebral thrombosis or pulmonary embolism. [The SC¹® indicates that this paper has been cited over 315 times since 1968.]

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"Shortly after my appointment as senior medical officer in charge of monitoring the adverse drug reactions reported to the Committee on Safety of Drugs (CSD), small numbers of suspected associations between oral contraceptive use and thromboembolic disease began to appear on the Committee's yellow cards. In the 12 months ending August 1965, the total of 16 reported deaths was very close to the 13 that would have been expected among the 400,000 women believed to have been using the pill at that time. If all deaths had been reported, use of the pill would appear to present no hazards, but lack of confidence in the completeness of the reporting led me to conduct, with the encouragement of the CSD, what proved to be the earliest study to show a significant relationship.

"During 1965 I had recruited a team of about 35 medically-qualified part-time field-workers and their first major assignment was to investigate deaths from thromboembolism of women aged between 20 and 44 occurring in the United Kingdom in 1966, identified by means of certificates provided by the Registrar General. At each interview with a general

practitioner they obtained details about use of oral contraceptives by the dead woman and by healthy controls in the same practice. By the end of August it became apparent that there was significantly greater use of the pill by the dead women.

"Because of the alarm that might have been caused by premature publicity, the CSD waited for the results of two further studies by the College of General Practitioners, commenced in July 1966, and by the Medical Research Council, commenced in December 1966. A meeting was arranged at the request of the Committee in January 1967 at which the results of the three studies were reviewed and in April a preliminary communication was prepared by a working group¹. This was the start of my long association with Martin Vessey and other workers in Oxford. By mid-1967 most of the fieldwork in the CSD was complete and Vessey accepted my invitation to become the coauthor and give expert epidemiological help in the preparation of the final report.

"After studying 385 deaths, we estimated the excess risk from pulmonary embolism and cerebral thrombosis attributable to use of the pill to be 1.3 deaths per 100,000 women aged 20 to 34, and 3.4 per 100,000 women aged 35 to 44, roughly a sevenfold risk among pill users. The risk of fatal myocardial infarction was not quite statistically significant, but if added to the above estimates brought the totals to 2.3 and 4.5 per 100,000 respectively.

"While studying voluntary reports to the CSD in 1966, I suspected that the preparations containing mestranol might carry a greater risk than those containing ethinylloestradiol; later it became apparent that the total dose of estrogen determined the risk and this hypothesis was developed in a further publication with Vessey and colleagues from Scandinavia in 1970². I have reviewed the history of these early pill studies elsewhere."³

1. **Medical Research Council.** Risk of thromboembolic disease in women taking oral contraceptives. A preliminary communication to the Medical Research Council by a sub-committee. *Brit. Med. J.* 2:355-9, 1967.
2. **Inman W H W, Vessey M P, Westerholm B & Engelund A.** Thromboembolic disease and the steroidal content of oral contraceptives. *Brit. Med. J.* 2:203-9, 1970.
3. **Inman W H W.** Role of drug-reaction monitoring in the investigation of thrombosis and "The Pill." *Brit. Med. Bull.* 26:3, 248-56, 1970.