

This Week's Citation Classic

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Inman W H W, Vessey M P, Westerholm B & Englund A. Thromboembolic disease and the steroidal content of oral contraceptives: a report to the Committee on Safety of Drugs. *Brit. Med. J.* 2:203-9, 1970. [Comm. on Safety of Drugs, Queen Anne's Gate, London; Dept. Med., Radcliffe Infirmary, Oxford, England; Swedish Adverse Drug Reactions Comm., Stockholm, Sweden; and Adverse Reactions Board, Danish Natl. Health Serv., Brønshøj, Denmark]

A study of reports of thromboembolic disease in women using oral contraceptives revealed that the greatest risk was in those using high doses of oestrogen. The demonstration of a dose-response effect confirmed that the Pill probably was a cause of thrombosis and led to the safer 'Mini Pill.' [The SC[®] indicates that this paper has been cited in over 360 publications since 1970.]

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"This study provided the first proof of a causal relationship between oral contraceptives and thrombosis. In 1964, I was invited by the late Sir Derrick Dunlop, the founder and chairman of the Committee on Safety of Drugs, to become its first Medical Assessor of Adverse Reactions. I was responsible to the Subcommittee on Adverse Reactions until 1980, when I became director of an independent Drug Surveillance Research Unit at the University of Southampton.

"From the very early days, reports of thromboembolism in young women suggested a possible association with oral contraceptives, and in 1965, I designed what was to become the first epidemiologic study to provide statistical proof of such an association.¹ This study involved all deaths of women between the ages of 15 and 44 who died from pulmonary embolism, or coronary or cerebral thrombosis, in England and Wales during 1966. By August of that year, sufficient material had been accumulated to demonstrate a positive association with oral contraceptives. We persuaded the Medical Research Council (MRC) and the College of General Practitioners to start additional studies late in 1966, and when these had demonstrated a similar association, we published a joint report to the MRC in April 1967.²

"Epidemiological studies prove associations but do not prove causation. Early in 1966, I had noticed among the spontaneous reports received on 'yellow cards' an unusual distribution of reports in relation to the oestrogen that had actually been taken by the patient. At that time, the market for oral contraceptives containing mestranol, or ethinyloestradiol, was divided in the proportion of 52 percent to 48 percent respectively; so were the reports of nearly all types of suspected adverse reactions, with the single exception of reports of venous thromboembolism. Here the distribution was in the ratio of 72 percent to 28 percent, a significant difference which I attributed to a possible thrombogenic effect of mestranol, since there was no other reason why thrombosis should have been reported selectively in women using this particular oestrogen.

"Somewhat distracted by doubts whether this was an intrinsic effect of the chemical or a dose-response effect, I withheld publication until many more reports had accumulated. By late-1969, it was clear that the dose rather than the nature of the oestrogen was the important factor. My results were reported to the Department of Health with the reservation that, at that time, I had not yet looked closely at the progestogen component. Unfortunately, but perhaps predictably, the material leaked to the press before any communication could be prepared informing prescribers of the added risk of high-dose oral contraceptives.

"Early in 1970, I flew to Denmark and Sweden, returning home with data on their reports and sales figures which showed exactly the same relationship.

"Although I was also responsible for the first epidemiological study to show a significant association between the Pill and venous thrombosis,¹ it was my work on the oestrogen dose effect, which clinched causality, that earned me the title 'Father of the Mini Pill'! Interest in the latter probably accounts for the frequent reference to this work. For some time, in the dark winter of 1970, I wondered whether the low-dose pills which were rapidly introduced would prevent conception or whether I might, inadvertently, have fathered rather more than I had bargained for!"

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. [Citation Classic. *Current Contents/Clinical Practice* 8(44):12, 3 November 1980.]
2. **Medical Research Council.** Risk of thromboembolic disease in women taking oral contraceptives. A preliminary communication to the Medical Research Council by a subcommittee. *Brit. Med. J.* 2:355-9, 1967.