

# This Week's Citation Classic

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**Sartwell P E, Masi A T, Arlhes F G, Greene G R & Smith H E.** Thromboembolism and oral contraceptives: an epidemiologic case-control study. *Amer. J. Epidemiol.* **90**:365-80, 1969.  
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**We made a case-control study of 175 women aged 15-44, hospitalized with idiopathic thromboembolism, and 175 matched hospital patients as controls. By interview, the relative risk of thrombosis for users of oral contraceptives within the month preceding onset was found to be 4.4. [The SC® indicates that this paper has been cited over 170 times since 1969.]**

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"This study can be traced to an innocent remark over cocktails that the problems of the Food and Drug Administration (FDA) in detecting and evaluating adverse drug reactions were epidemiological. This led to an appointment in 1965 to the FDA's Advisory Committee on Obstetrics and Gynecology, whereupon I learned that the most serious question then before the Committee was whether use of oral contraceptives was a cause of thrombophlebitis, pulmonary embolism, and other intravascular clotting. Although several erudite committees had already debated this question, there were no answers because no one had begun to collect really useful data to test the hypothesis.

"I outlined a proposal for a case-control (retrospective) study, whereupon the representatives of the drug industry who attended the meeting drafted a commentary explaining why it wouldn't work. Despite this opposition, the agency supported the study wholeheartedly.

"Alfonse Masi, who doubled as epidemiologist and internist, and I recruited a

field team, including Federico Arthes, internist, and Helen Smith, project supervisor. Later, Gerald Greene joined us on loan from CDC. Others, named in the paper, provided invaluable assistance

"We determined to include only women with no apparent reason to develop intravascular clotting, and spent considerable time polling authorities as to what conditions should be considered cause for rejection of a case. We found it necessary to reject the great majority of patients for this and other reasons. This selectivity necessitated the collaboration of 43 hospitals in five large eastern cities. After we had begun work we learned that W.H.W. Inman, R. Doll, M.P. Vessey, and others had similar studies under way in the UK.<sup>1,2</sup> They were able to complete and publish their investigations well before we did.

"Subjects (women aged 15-44 meeting the study requirements) were interviewed at home by employees of a survey research company using a pretested structured questionnaire. We devised special methods to obtain complete medical and reproductive histories, and to have the subjects identify the drugs taken, and over what period. There were 350 subjects (175 cases, 175 controls)

"The study yielded an overall 'relative risk' of 4.4 (idiopathic thrombosis  $4\frac{1}{2}$  times more frequent in users of OCs than nonusers) For deep thrombosis, pulmonary embolism alone, and intracranial lesions, the risk ratio was significantly increased. A subsequent paper<sup>3</sup> provided further information as to our methods and results.

"Why so many citations? Certainly because of the importance of this finding to many millions of women and their physicians and because this was the first study of its kind done in the US. The study has been vigorously challenged, but enough work has been done by others to consider the hypothesis established."

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.
2. **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.
3. **Sartwell P E.** Oral contraceptives and thromboembolism: a further report. *Amer. J. Epidemiol.* **94**:192-201, 1971.