

The question arises as to which component of the oral contraceptives is responsible for the intravascular changes. Vessey and Doll were unable to detect any differences suggesting that one formulation carried more risk than another. This study indicated that the sequential products were more hazardous. Daniel and others in Cardiff, Wales (10) found that the suppression of lactation in puerperal woman by administration of the synthetic estrogen diethylstilbestrol was associated with an increased incidence of thromboembolism, at least among women over 25 years of age, as compared to puerperal women who were lactating. This was confirmed by Tindall (11) who reported that suppression by another estrogen, ethinyl estradiol, increased the incidence threefold. These findings, together with the known effects of estrogen on clotting mechanisms as summarized by Dugdale and Masi (12), suggest rather strongly that the estrogen is the more important agent involved in these adverse effects.

Even when the relative risk for oral contraceptive users has been established, it is necessary to estimate what proportion of initial attacks of idiopathic thromboembolism are attributable to oral contraceptives. This depends on the number of women who use the hormones and the level of incidence in non-users. The following approach was taken to make the estimate: the difference between the number of discrepant pairs in which the case only was a user, minus the number in which the control only was a user, was 57 minus 13, or 44. This may be considered an estimate of the actual number of individuals among the cases whose illnesses were attributable to the hormone. They constitute $44/175$ or 25.1% of the total cases. This figure is of course subject to sampling error as well as the errors involved in the fact that the case series are not a probability sample of all the cases of thromboembolism in the community and the controls are not a probability sample of women in the same population. Nevertheless the estimate does give emphasis to the fact that the majority of cases of spontaneous, idiopathic thromboembolism, including many cases among hormone users, are not attributable to the hormones.

SUMMARY

A retrospective study of thromboembolism in females of reproductive age was conducted in five American cities. Cases were 175 women aged 15-44 discharged alive from 43 hospitals, after initial attacks of idiopathic thrombophlebitis, pulmonary embolism, or cerebral thrombosis or embolism. Idiopathic cases constituted only a small fraction of total thromboembolism patients. The 175 hospital controls were matched pair-wise with the cases on hospital, residence, time of hospitalization, race, age, marital status, parity and pay status. Both groups were free of chronic conditions either associated with thromboembolism or constituting contraindications to pregnancy, and were presumably fertile. They were interviewed to provide information on their use of oral contraceptives prior to hospitalization. Sixty-seven cases and 23 controls had used these products until within one month before they were hospitalized; 11 cases and controls had discontinued use earlier. Duration of use did not affect the risk. There were 57 case-control pairs in which only the case had used an oral contraceptive within one month compared to 13 in which only the control had done so. The relative risk of thromboembolism for the users is estimated to be 4.4 times that of nonusers. The risk was higher for users of sequential products. It is estimated that 25 per cent of the cases in this series were attributable to oral contraceptives.

ADDENDUM

The interesting observation has recently been made of a deficiency of patients in blood group O among cases of thromboembolism in women, and especially in women who were taking oral contraceptives, as compared to controls.⁶ This difference in blood group distributions, although interesting, requires further substantiation and is not, in our opinion, large enough to warrant any modification in recommendations for administration of oral contraceptives at present.

⁶Jick, H., Slone, D., Westerholm, B., Inman, W. H. W., Vessey, M. P., Shapiro, S., Lewis, G. P., and Worcester, J. Venous thromboembolic disease and ABO blood type. *Lancet* 1:539, 1969.