

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

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## Oral Contraceptives and Hypercoagulation

Diana B. Petitti, MD  
Director of Research and Evaluation  
Southern California Permanente Medical Group

**H&O** What is the historical background on the connection between oral contraceptives and hypercoagulability?

**DP** Oral contraceptives were first approved for marketing in the United States in 1961. Less than a year later, published reports were showing an increased incidence of venous and thrombotic events among young women taking oral estrogen-containing contraceptives. These findings came as a surprise; there had been concern that oral estrogen contraceptives might increase the risk of cancer, but there was no suspicion that they might cause excess clotting or hypercoagulability. A number of epidemiologic studies followed in the mid 1960s that confirmed this link, and it was determined that estrogen was the underlying cause.

**H&O** Were the doses of estrogen included in the earliest oral contraceptives higher than what is used today?

**DP** Yes. The earliest oral contraceptives used a very high dose of estrogen compared to what is used today. The first agents used 10 mg of progestin; today, oral contraceptives contain approximately 0.3 mg. Even in the early 1970s, the most widely used birth control pills contained 80 mcg of mestranol, which is roughly equivalent to 80 mcg of ethinyl estradiol. The first pills contained 500 mcg of the estrogen mestranol; this amount was decreased quickly to 100 mcg and, in the 1970s, to 80 mcg. These formulations are not used anymore. Oral contraceptives now in widespread use contain less than 50 mcg of the equivalent estrogen, ethinyl estradiol.

**H&O** How did the use of estrogen in oral contraceptives change as these findings were reported?

**DP** The scientific community began to realize that high doses of estrogen were not only associated with clotting and hypercoagulability, but also were not necessary to affect fertility; this hormone was added to reduce the likelihood of breakthrough bleeding and to create menstrual periods by stimulating the uterus. It was thought that the withdrawal bleeding that occurred when oral contraceptive use was stopped was somehow more “natural.”

**H&O** What cardiovascular problems are seen today with oral contraceptive use?

**DP** The vascular diseases most highly associated with oral contraceptives are venous thromboembolic events, including thrombophlebitis and pulmonary embolism. However, this risk has certainly decreased over the years; in the 1960s, the risk was 8–11 times higher among people taking oral contraceptives versus those not taking oral contraceptives, whereas today the risk is only approximately 2–4 times higher.

Oral contraceptives are also linked with ischemic and thrombotic stroke. The relative risk for these conditions is 2–4 among women with hypertension. However, among women who do not have hypertension and do not smoke, the increase in risk is negligible if there is an increase at all. Birth control pills have also been associated with an increased risk of myocardial infarction among women who smoke.

**H&O** Do the venous thromboembolic events and arterial thrombosis associated with birth control pills tend to be acute or chronic?

**DP** The events are acute and the most essential information to obtain is how much damage has been caused and how much of this damage carries over. For example, if an individual experiences an ischemic stroke and part of the brain is necrotic, then there will be a chronic injury. With venous thromboembolism, once it occurs for the first time, there is always a possibility of recurrence. However, if an individual recovers from a venous thromboembolic event, there is usually no residual effect. When acute myocardial infarction occurs, the amount of damage done to the heart must be assessed.

**H&O** Should women with a history of venous thromboembolic events be allowed to use oral contraceptives?

**DP** The data on this subject are inconclusive at present, but, in general, the package inserts for oral contraceptives warn that a prior history of venous thromboembolic events, stroke, or arterial thrombosis is a contraindication.

**H&O** Could you further discuss the risks associated with the birth control pills available today?

**DP** Almost all the research done has been with the combined estrogen/progestin oral contraceptives. With the currently available agents, which are low in estrogen and progestin, the likelihood of any of these conditions occurring in a woman who is healthy and of reproductive age is quite low in absolute terms—the excess is measured in events per 100,000 women. As already mentioned, the combination of cigarette smoking and use of oral contraception is associated with a higher risk, and the risk of stroke among individuals using oral contraception is linked with hypertension. There is some research suggesting that obese women are also at particular risk of experiencing thrombotic events while taking oral contraceptives. Venous thromboembolism is the only event for which no clear risk factors have been identified. Such events can occur unexpectedly in women taking birth control pills, regardless of the absence of other identified risk factors.

**H&O** Are there inherited factors that are associated with an increased risk?

**DP** Yes. The most well-studied inheritable trait is the Factor V Leiden mutation. This mutation has been associated

with an increased risk of venous thromboembolic events and is relatively common among white European populations; there are few data available about the prevalence of this mutation in other populations. Several studies show that women who have this mutation and who use oral contraception have an even higher risk of venous thromboembolic events.

The methylenetetrahydrofolate reductase (MTHFR) mutation has also been studied in this context. This mutation has not been consistently associated with an increased risk of venous thromboembolism overall or in oral contraceptive users. In our study of this mutation, we found no specifically associated risk among women with this mutation who were taking oral contraceptives. It should be noted that the MTHFR carriers were heterozygotes.

The prothrombin mutation has also been studied. This mutation is associated with an increased risk of venous thromboembolism, but there does not appear to be an additional increase in risk associated with oral contraception.

**H&O** Has screening been considered as a way to identify women at risk of venous thromboembolism before they begin taking oral contraceptives?

**DP** The question of whether or not to screen for Factor V Leiden among women considering oral contraceptive use has been quite controversial. These women are at increased risk for venous thromboembolism overall and this increase is exacerbated by oral contraceptive use. However, the screening test is costly and the likelihood of venous thromboembolism occurring is not high enough to justify screening every woman who contemplates using oral contraception.

There has been some discussion of obtaining a family history regarding venous thromboembolic events and then screening only those women with a relevant family history. However, a family history of venous thromboembolism is not a good predictor of the presence of a Factor V Leiden mutation. Currently, it is not routine procedure to screen for Factor V Leiden, nor to ask for a family history of venous thromboembolism and then screen selectively.

**H&O** Is it only the estrogen component that has been linked with adverse events, or is progestin also associated with adverse hematologic events?

**DP** Estrogen dose is related to the risk of venous thromboembolism. Recent data have shown that the progestin

type modifies the risk of venous thromboembolism at a fixed dose of estrogen. Some progestins, specifically gestodene, which is not used in any pills ever marketed in the United States, and desogestrel, which is contained in pills marketed here now, double the risk of venous thromboembolism compared with older progestins.

This finding came as a surprise to many clinicians, as it had always been thought that estrogen was the sole determinant of the risk of thrombotic and venous thrombotic events.

### **H&O** What is the mechanism behind the association between hormones and venous thromboembolism?

**DP** Research to identify the exact mechanism has been going on for decades, but no clear answer has been found. There has been much interest in activated protein C resistance, which is affected by the Factor V Leiden mutation.

It would be helpful to understand the mechanism at play so that we might be able to predict which women are likely to experience these events and so new compounds could be tested for their likelihood to increase or decrease this risk. However, this area of research has not been very fruitful thus far, and for now we must accept that the phenomenon occurs, regardless of the lack of a clear understanding of why it does.

### **H&O** Can you discuss recent findings on the risk of ischemic stroke as it relates to thrombophilia in women receiving oral contraceptives?

**DP** Dr. Martinelli and colleagues recently reported the results of an investigation into the interaction of oral contraceptives and thrombophilia in ischemic stroke. In a case-control manner, they looked at women who had an ischemic stroke before the age of 45. It was found that oral contraceptives doubled the risk of ischemic stroke in the first 6–18 months of use. The presence of hyperhomocysteinemia increased by 3.5-fold. It was also found that the risk of ischemic stroke in oral contraceptive users was 13-fold higher in women who were also carriers of Factor V Leiden and 9-fold higher in those who also had hyperhomocysteinemia.

### **Suggested Reading**

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