Contraceptives and Thrombosis: An Intertwined Revolutionary Road

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Semin Thromb Hemost 2024;50:91–95.

Abstract

The development of oral contraceptives (OCs) began in 1921 and continued in the following years until the first regulatory approval from the Food and Drug Administration was granted in 1960. However, it took several years to realize that OCs presented an important but not frequent risk of venous thrombosis. Several reports ignored this dangerous effect and only in 1967 the Medical Research Council clearly stated this as an important risk. Later, research led to the formulation of second-generation OCs containing progestins, which nevertheless presented an increased thrombotic risk. In early 1980s, OCs containing third-generation progestins were introduced into the market. Only in 1995, it became clear that these new compounds induced a higher thrombotic risk than that related to the second-generation progestins. It appeared clear that the modulating action of progestins was against the procoagulant activity of estrogens. Lastly, at the end of the 2000s, OCs containing natural estrogens and a fourth-generation progestin (dienogest) became available. The prothrombotic effect of those natural products was not different from that of preparations containing second-generation progestins. Moreover, research over the years has produced much data on risk factors associated with OCs use such as age, obesity, cigarette smoking, and thrombophilia. These findings allowed us to better assess the individual thrombotic risk (both arterial and thrombotic) of each woman before offering an OC. Furthermore, research has shown that in high-risk people the use of single progestin is not dangerous as far as thrombosis is concerned. In conclusion, the OCs road has been long and difficult but has led to a great and unthinkable scientific and social enrichment since the 1960s.

Keywords
- estrogens
- progestins
- oral contraceptives
- thrombosis

The Beginning of the History

The history of oral contraceptives (OCs) began in 1921 when Ludwig Haberlandt, an Austrian Professor of Physiology, discovered a temporary hormonal contraception in female animals after transplanting ovaries from pregnant animals[1] (►**Fig. 1**). From 1923, he enforced his idea on the concept that procreation would have been a voluntary and deliberate

article published online March 13, 2023

Issue Theme Celebrating 50 years of Seminars in Thrombosis and Hemostasis —Part III; Guest Editor: Emmanuel J. Favaloro, PhD, FFSc (RCPA)

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0043-1764382.
ISSN 0094-6176.

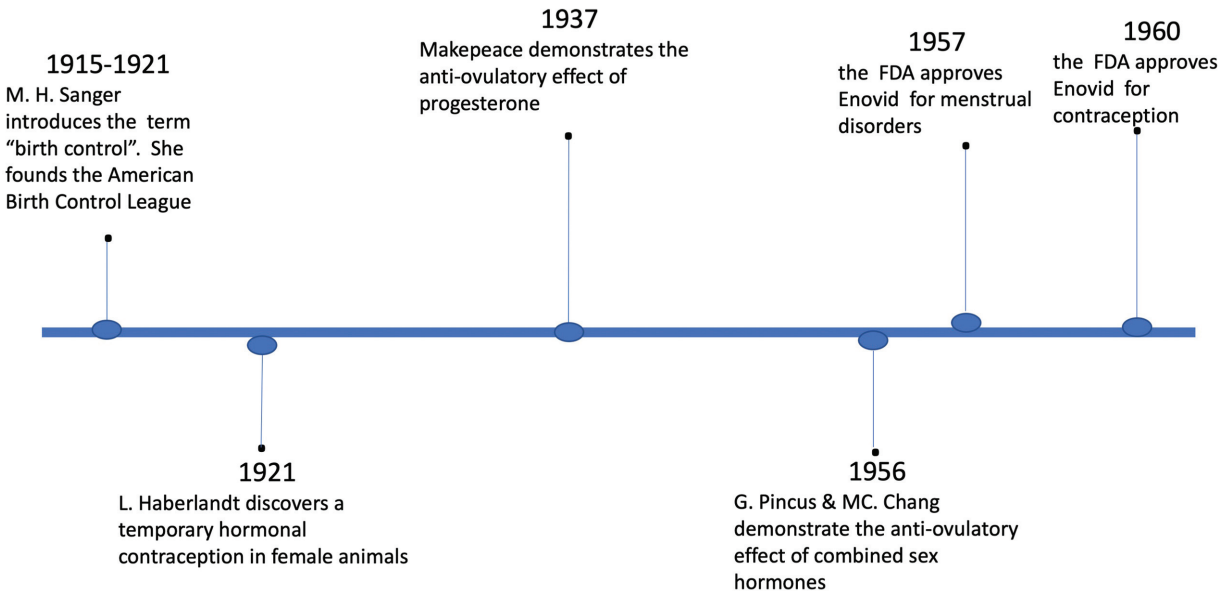

Fig. 1 Milestones in the history of oral contraceptives: from the introduction of the term "birth control" to the first pill approval by FDA.

act after having confirmed his early pioneering results. However, at that time, he was harassed because of his views on reproductive biology, until his tragic death by suicide in 1932.[2]

In 1937, Makepeace and coworkers[3] demonstrated the antiovulatory effect of progesterone.

However, the researcher who played the initial pivotal role in the development of OCs was Margaret Higgins Sanger, an Irish American nurse, family rights activist, sex educator, and writer. In the years from 1915 to 1921, she introduced the term "birth control" and founded the American Birth Control League. A famous and central Higgins' statement was the following: "Woman must have her freedom—the fundamental freedom of choosing whether or not she shall be a mother and how many children she will have"[4].

In the early 1950s, she approached Gregory Pincus, a reproductive biologist, who developed projects on OCs research, funded by her friend Katherine McCormick.[5] In 1956, Pincus and especially one of his coworkers, Min-Chueh Chang, demonstrated the antiovulatory effect of combined sex hormones at the Worchester Foundation for Experimental Biology.[6,7] Furthermore, they were able to produce the first combined OC, Enovid (5 mg norethynodrel and 75 µg ethinylestradiol 3-methyl ether), later manufactured and marketed by Seale Company. Clinical trials were done in Puerto Rico, since in the United States contraception was still considered a crime. In 1957, the Food and Drug Administration (FDA) approved Enovid only for menstrual disorders, extending its use to contraception in 1960[8] (►**Fig. 1**).

However, it was 10 years later that nonmarried women were allowed to access OCs in the United States.[8]

The History of Oral Contraceptives—Associated Venous Thromboembolism

In 1961, Jordan and Anand reported in The Lancet[9] the clinical history of a nurse, 40 years old, who suffered from a bilateral pulmonary embolism and infarction after having taken Enovid for endometriosis. The authors did not consider a possible hypercoagulable state induced by Enovid and the age of the patient. They reported dehydration, secondary to vomiting as the cause of the thromboembolic event.

The final FDA report on Enovid, published in 1963 by the ad hoc Advisory Committee for the evaluation of a possible etiologic relation with thromboembolic conditions concluded that there was no significant increase in the risk of thromboembolic death from the use of Enovid.[10] The final results of this FDA report were challenged by severe criticism of statistical methods used in data analysis, to conclude a nonsignificant difference in the mortality rates between Enovid users and nonusers.

The Advisory Committee reported 12 deaths from thromboembolism among 1 million "women users" of Enovid during 1962 versus 8.4 in the general population. Surprisingly, this difference was not found to be significant, but when age groups were taken into account, an increased risk for women over 35 years was found.[11] Even this important finding failed to stimulate the Committee to provide a warning message. Again, no effort was undertaken to evaluate the risk of a woman who had taken Enovid for a few days compared with that of another who had consumed the drug for a much longer time. In the end, all these crucial points at that time were totally ignored.

More surprisingly, in 1964 Tyler did not report any increase in the thromboembolism event rates during the analysis of 8 years of contraception use.[12] He described his experience with two different compounds of OCs, the first one containing 10 mg of norethisterone with a variable amount of mestranol (ethinyl-estradiol, 3-methyl ether) not exceeding 0.06 mg, the second one containing 2.5 mg of norethynodrel with 0.1 mg of mestranol.

In the 8 years' of experience at the Los Angeles Planned Parenteral Center, no cases of "thrombophlebitis or

embolism" were detected in a sample of 5,000 women using several compounds, as Tyler pointed out. He concluded that no studies were able to obtain data demonstrating a tendency toward an increased tendency for the blood to clot. Accordingly, he concluded that no new attempts would have been made to further analyze the "contraception-thrombosis" topic.

However, Thomson and Poller[13] in 1965 found an increase in factor VII levels in women using various OCs from the 3rd month of use, onward. They concluded that their results were similar to those found during pregnancy and puerperium; conditions already known to represent a high risk of venous thromboembolism (VTE).[14]

The authors of that study were influenced by previous reports indicating an association between contraception and arterial thrombosis[15] and by the findings of Egeberg and Owren, who demonstrated a marked hypercoagulable state in a small group of women taking Enavid, the brand of Enovid in Europe.[16] Many years later, the definite prothrombotic role of OCs was demonstrated. These drugs induce an increase in factor II (prothrombin), factor VIII, factor IX, and fibrinogen parallel to a decrease of the natural anticoagulants such as antithrombin, protein C, and protein S so provoking an unbalance between blood coagulation activity and its negative feedback control. The final outcome is an increased risk for VTE.[17]

Eventually, in 1967, a communication from the Medical Research Council[18] reported preliminary results coming from three retrospective studies demonstrating an association between OCs and VTE. These important findings led to the progressive reduction of the dosage of ethinylestradiol in combined OCs from 50 to 30, 20 down to 15 µg. Nevertheless, OCs would still induce a prothrombotic effect. The development of levonorgestrel allowed the reduction of progestin dosage. A second generation of progestins then began to be offered to the market at the end of the 60s.[19] Afterward, doses of levonorgestrel ranging from 250 to 100 mg, combined with 50, 30, or 20 mg ethinylestradiol, were still being used. OCs containing levonorgestrel showed a mean relative risk (RR) of approximately 3 in comparison with nonusers, thus confirming the prothrombotic effect of these drugs.[20]

In the 1980s, a third generation of the combination estrogen/progestin entered the market.

The progestins norgestimate, desogestrel, and gestoden were introduced as alternatives to norgestrel/levonorgestrel. The aim was to propose new compounds with significantly fewer undesirable side effects such as nausea, weight gain, and mastalgia. An important point claimed at that time was a more favorable lipid metabolism,[21] thus concluding that the new generation progestins would have had no impact on atherogenesis.[22] Nevertheless, in 1995, it was proven that the new OCs, including the fourth generation progestins such as drospirenone, further increased the risk of VTE by 1.5 to 3-fold when compared with the second generation of progestins[23] (►**Fig. 2**).

In 1995, an important multinational World Health Organization hospital-based case-control study on the risk of VTE was performed.[24] The final results were gathered from data from nine countries, involving 769 cases and 1,979 age-matched hospital controls. Women treated with desogestrel and gestodene were compared with levonorgestrel users. The respective odds ratio (OR) were 2.4 (1.3–4.6) and 3.1 (1.6–5.9). The risks were even more pronounced when adjusted for body mass index, reaching 3.4, 7.3, and 10.2 for levonorgestrel, desogestrel, and gestodene in comparison with nonusers, and 2.2 and 3.0 for desogestrel and gestodene compared with levonorgestrel, respectively.

In 2018, a meta-analysis considered 17 studies and 23,595,640 women. The reference was levonorgestrel with 30 to 40 µg ethinylestradiol. OCs containing desogestrel, gestodene, and drospirenone, all with 30 to 40 µg estrogen, showed a higher RR but the RR increased by 30, 39, and 40%

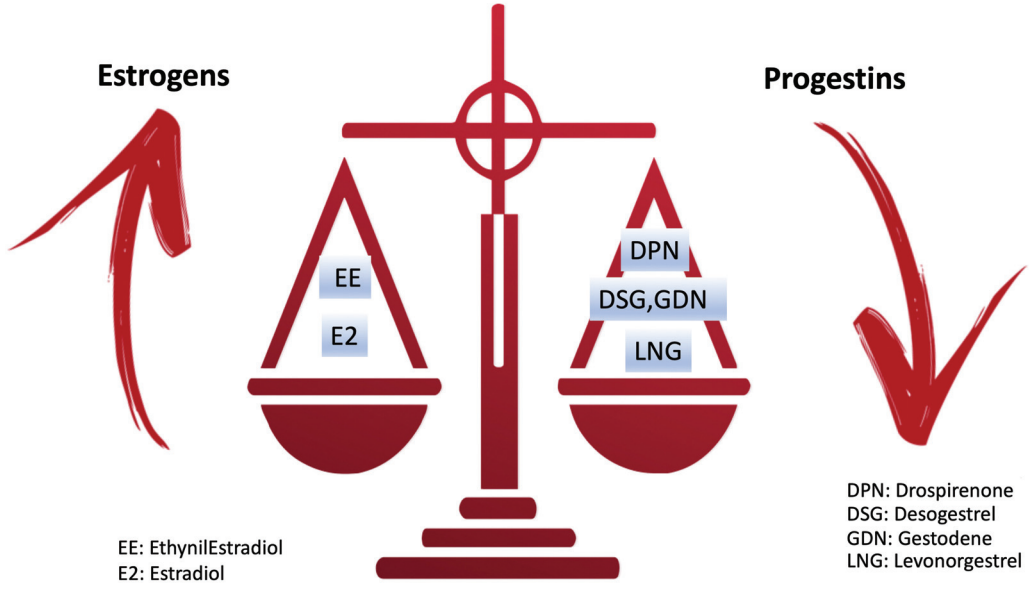

Fig. 2 Estrogens and progestins available on the market: the risk of venous thromboembolism varies according to different combinations.

when 20 µg of ethinylestradiol was combined with desogestrel, gestodene, and drospirenone, respectively.[25]

The Pathophysiology of Oral Contraceptives—Associated Venous Thromboembolism and the Novel Concept of Estrogenicity

The concept of "estrogenicity" was introduced with the aim of explaining these prior findings. Estrogenicity may be identified with the activity of sex hormone-binding globulin (SHBG), a liver protein whose levels increase in the blood after estrogen administration, depending on the dosage. On the contrary, the SHBG level decreases if progestin is added.[26] Thus, it appeared that progestins were able to modulate the prothrombotic effects of estrogens. Odlind et al[27] found that desogestrel and gestodene induce an increase in SHBG levels between 200 and 300% and cyproterone acetate further amplified this phenomenon (300–400%). Also, other combined progestins, norgestimate, drospirenone and dienogest increased SHBG ranging from 150 to 300%.

In contrast, levonorgestrel was found to increase SHBG much less, 50%, thus showing, on biochemical grounds why the risk for VTE is greater when the third- and fourth-generation progestins are employed in comparison with those of the second generation.

In 2009, research on this topic achieved further important results. Estradiol was proposed to the market as an alternative to ethinylestradiol in the combined OCs.[28] Estradiol presented several advantages in comparison with ethinylestradiol; it did not exert a negative effect on hepatic and metabolic parameters and did not negatively impact blood pressure. Moreover, parameters related to a hypercoagulable state were found unchanged after the administration of estradiol (with dienogest), while they appeared increased after ethinylestradiol (with levonorgestrel).[29]

Other studies confirmed these findings[30] so that the International Active Surveillance study "Safety of Contraceptives: Role of Estrogens" (INAS-SCORE), a large international prospective, controlled, noninterventional cohort study was planned. This study started in 2009 and provided final results in 2016.[31] A total of 53,750 women were recruited by 1,327 centers. The follow-up was up to 5.5 years (mean 2.1 years). The occurrence of VTE and other cardiovascular events in users of estradiol valerate/dienogest was not different compared with other estrogens with levonorgestrel preparations.

The Role of Concurrent Risk Factors

After having recognized the prothrombotic effect of OCs, it became important to study also risk factors associated with their use. It thus appeared important to develop research examining the effect of age, obesity, smoking, and thrombophilia. The results of this large research demonstrated that women's age is important to consider since the thrombotic risk significantly increases after 35 years in comparison with women aged 15 to 19 years: RR of 4.01 (3.32–4.87). The RR is further increased in women aged 44 to 49 years (6.58, 5.43–7.99).[32]

Table 1 Factors increasing venous thromboembolism risk with use of combined oral contraceptives

Risk factor
Age
Body mass index
Smoking
Thrombophilia
Comorbidities

The risk for VTE in obesity and OCs is also reported to be high: approximately 10-fold after a review of a large literature database.[33]

Smoking has been associated not only with a higher risk of VTE[33], but also with a high risk of myocardial infarction[34] (OR = 13.6, 7.9–23.4). Finally, thrombophilia, especially related to the most frequent mutation of the general population, factor V Leiden or Prothrombin G20210A, was found to further increase the thrombotic risk: OR = 5.89 (4.21–8.23), as shown by a systematic review and meta-analysis published in 2016.[35] Therefore, a precise definition of these risk factors is helpful in finding the best choice when offering OC (►**Table 1**).

Finally, the research on this topic added an important and practical point related to the use of a progestin only to be proposed to women with a high thrombotic risk. In 2018, a systematic review showed that the RR for VTE (1.06, 95% confidence interval [CI]: 0.70–1.62), myocardial infarction (0.98, 95% CI: 0.66–1.47), and stroke events (1.02, 95% CI: 0.72–1.44) were not statistically significant when comparing oral progestins users with non-users.[36]

Conclusions

The OCs story had a difficult beginning, as with all new and revolutionary events. At the time in which discussion on birth control began, the mindset was completely closed to the thought that women could manage their sexuality, because it was believed, according to the doctrine of Saint Augustine, that sexual intercourse should only be aimed at procreation. But the history of OCs also passed through the initial ignorance of the scientific committees that disregarded the prothrombotic effect of OCs, falling into errors of statistical methodology noticed but borne by other scientists.

The research finally confirmed that the OCs were promoters not only of venous thromboembolic events but also of arterial. Surprisingly, the scientific community then had to realize that third-generation progestins were associated with a further increase in thrombotic risk compared with second-generation progestins.

Only in the past 10 years, has it come to propose natural estrogens, such as estradiol, that have reported the thrombotic risk very close if not lower than that of the OCs of the second generation. Estradiol and dienogest are now the

most recommended OCs preparations, even if the thrombotic risk has not completely disappeared. Attention was then paid to progestins that do not have a prothrombotic effect but that, when administered with estrogens, modulate the hypercoagulable effect.

Finally, the history of OCs has been enriched with a lot of data regarding different risk factors that, when carefully evaluated, allow us to better address the choice of OC in the individual woman.

In conclusion, the OC road has been long and difficult but has led to a scientific and social enrichment really unthinkable since the 60s.

Conflict of Interest
None declared.

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