EDITORIAL OPEN ACCESS

Fifty-five years on: Where is the contraceptive pill?

Iñaki Lete

Combined oral contraception is one of the contraceptive methods most widely used worldwide. The first hormonal contraceptive, Enovid, was introduced in the USA on the 11 May 1960. The contraceptive pill was designed for preventative and not curative care, and its availability meant, for women and humanity, significant progress in medical but also social and human rights terms. Each pill of Enovid contained 75 μg of mestranol and 5 mg of noretynodrel. The pill was initially well accepted due to its high efficacy for avoiding unwanted pregnancies, but soon after its introduction, evidence emerged that it might be associated with severe adverse effects, in particular thrombosis. The first reports of thrombotic events found an association with the dose of oestrogens. Since then, it has been well established that one of the adverse effects of combined hormonal contraceptives is an increased risk of developing venous thromboembolism in its two clinical presentations: deep vein thrombosis (DVT) and pulmonary embolism (PE).

Combined hormonal contraceptives can produce a hypercoagulable state with an increased production of fibrin due to changes in both procoagulant proteins and natural anticoagulants. The primary cause of these changes is the oestrogenic component of the contraceptive [1], while progestogens tend to counteract this action, with an intensity that depends on the type [2]. The strongest effect of oestrogens on the coagulation factors is the induction of acquired resistance to activated protein C.

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Received: 09 September 2015
Published: 02 November 2015

Efforts were launched to develop contraceptives that were safer for women and, with this, the dose of ethinyl estradiol (EE) started to be reduced. From the initial 75 μg of mestranol, the dose has dropped over the years to 30, 20 or even 15 mg of EE. At the same time, research has focused on the development and synthesis of new and more selective progestogens, in order to reduce the adverse effects associated with modification of glucose and lipid metabolism.

Fifty-five years on, after the investment of many millions of dollars and extensive research, I ask myself: are current contraceptive pills really safer and more effective than those of 1960s?

Regarding their safety, we know that the administration of exogenous oestrogens increases the risk of thrombosis, compared to that in women who do not use this type of product. This is a risk that women who want to use combine hormonal contraception must accept, and that, in any case, is much lower than the risk of thromboembolism associated with pregnancy, delivery and the puerperium. Further, many epidemiological studies have demonstrated that the risk of DVT is greater in women on contraceptives containing new progestogens (third and fourth generations), compared to those on pills containing "old-type" progestogens (second generation) [3]. Despite controversy that these studies may have generated in the scientific community, health agencies recommend the prescription of combined oral contraceptives containing levonorgestrel, norethisterone or norgestimate [4]. The conclusion is that, in terms of the safety of combined oral contraception, little has changed in 50 years.

Another issue related to contraception that is of concern to health professionals is the effectiveness of the methods. Here, it is important to distinguish between efficacy and effectiveness. Efficacy means the ability of a contraceptive method to prevent pregnancy when used perfectly, while effectiveness is related to typical use of the contraceptive. According to data from researchers in the USA, while the perfect use failure rate of combined oral contraceptives among users is 0.3% per year, the typical use failure rate (effectiveness) is as high as 9% per year [5]. In the case of the pill, this difference between efficacy and

effectiveness is due to treatment adherence. Despite the evolution of pills, with reductions in the hormone doses, we have not been able to significantly improve adherence to the treatment over the years. A recent study carried out in five different countries demonstrated that only 22% of women never forgot to take their pill [6]. In accordance with the results of a Cochrane review, few strategies have worked to improve adherence to daily doses [7], and in the field of contraception, one measure that has shown to be effective is the use of methods that do not rely on taking daily doses [8].

What is then the current situation of the contraceptive pill? On the one hand, the recommendations are to use pills with androgenic progestins, which many women, especially in European Mediterranean regions, are not willing to take due to potential negative impact on the skin, including the triggering of acne. On the other hand, there are still high rates of unwanted pregnancies associated with poor adherence and hence low effectiveness. Can research improve this situation?

First, we must emphasize that venous thromboembolism is directly related to the oestrogenic component of the contraceptive, and hence methods that rely on progestogens are not associated with a greater risk of developing this disease [9]. Hence, the use of estradiol (E2) instead of EE may make it possible to decrease the risk associated with combined oral contraception. A recent review of the effect of the most commonly used contraceptives (EE + levonorgestrel, EE + drospirenone) and oral contraceptives containing estradiol (E2 + dienogest, E2 + nomegestrol acetate) on hemostasis parameters, a subrogate marker for venous thromboembolism risk, has found a lower level of activation of the procoagulant factors and greater activation of anticoagulant factors in women who use oral contraceptives based on E2 [10]. Despite a lack of results from epidemiological studies showing a lower incidence of DVT in women using pills based on E2, data available indicating less impact on coagulation parameters encourages us to believe that the use of a natural oestrogen improves clinical safety. Moreover, it can be expected that the impact on coagulation parameters would be even lower if E2 were administered by a non-oral route (transdermal or vaginal) [11].

Secondly, regarding the effectiveness of combined oral contraceptives, a large prospective study has already demonstrated that is it better to use formulations that contain a long half-life progestogen that reduces the hormone-free period [12]. Unfortunately, women today are still using the classical regimen of 21 plus 7 days, though it has been shown to be less effective and associated with a higher rate of side effects [13]. This explains why, despite changes that have taken place, the rates of effectiveness of combined oral contraceptives continue to be similar to those of 50 years ago.

Hence, the current situation seems to be that the most modern pills, based on EE are less safe than the older ones and that the effectiveness of the method, which relies on adherence, has not improved. This reality warrants deep reflection by all those involved in contraceptive strategies: governments and related bodies, the pharmaceutical industry, health professionals and users, in order that, together we achieve real progress in combined hormonal contraceptives and such progress would likely come through the use of E2 in place of EE.

Keywords: Combined oral contraceptives, Ethinylestradiol, Estradiol, Venous thromboembolism

How to cite this article

Lete I. Fifty-five years on: Where is the contraceptive pill. Edorium J Gynecol Obstet 2015;1:14–16.

Article ID: 100004G06IL2015

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doi:10.5348/G06-2015-4-ED-4

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Author Contributions

Iñaki Lete – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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