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Oral contraceptive pills: advances and progress over the last 50 years

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"Hormonal contraception … represents the class of compounds most widely tested in clinical pharmacology and epidemiology."

Hormonal contraception has been successfully utilized for more than 50 years and represents the class of compounds most widely tested in clinical pharmacology and epidemiology.

This should not surprise since contraception is not aimed at combating a disease, where often the occurrence of some side effects can be tolerated in view of therapeutic benefits. On the contrary, hormonal contraceptives are mostly administered to healthy young women wishing to avoid pregnancy at a given time in their lives; obviously, these women are neither happy nor willing to impair their present or future health in order to prevent gestation.

This is why every time even a rare adverse event has been identified, this has been invariably followed by a wave of panic that subsided only years later, after either modification of dosage or the marketing of new, improved progestational agents [1].

The first pill scare dates back to the early 1970s when evidence began to appear linking combined hormonal contraceptives to an increase in the occurrence of venous thromboembolism [2]. The appearance of such epidemiological evidence had a major impact because the adverse event was immediately linked to the estrogenic component. As a consequence, the pharmaceutical industry went to work and within 20 years the daily dose of ethinyl estradiol was decreased from 50 to 30 mg and even 20 mg per day. In addition, in the 1970s, animal testing in female beagle dogs led to the withdrawal from the market of a number of good synthetic progestin derivatives of progesterone. It took millions of dollars and 20 years to prove that the beagle model is grossly inadequate to test the carcinogenicity of progestational compounds. Today some of these compounds have been reintroduced with good results.

"…in the 1980s, studies linked the use of some progestins to disturbances in lipid metabolism, with a possible … increase in arterial diseases."

Then, in the 1980s, studies linked the use of some progestins to disturbances in lipid metabolism, with a possible (although not documented) increase in arterial diseases [3]. This discovery led to the introduction of new, very potent and 'metabolically neutral' synthetic progestins (desogestrel, gestodene and norgestimate) making hormonal contraception even safer, although – in the 1990s – WHO-sponsored studies found evidence that these new steroids may in fact slightly increase the risk of thromboembolism compared with the classic levonorgestrel-containing pills [4]. Interestingly, recent studies found that even one of the newest marketed progestins (drospirenone), a component of the latest generation of oral contraceptives, may increase by two- to three-fold the risk of venous thromboembolism [5,6]. Both the US FDA and the European Medicines Agency are currently reviewing and updating the product information on oral contraceptives containing these new steroids. In addition, the FDA has announced that "Data from an additional, large, FDA-funded study on hormonal contraceptives is also being finalized and reviewed" [101].

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More recently, even the false 'dogma' of the 'lowest possible dosage' has been challenged. In fact, whereas it is true that lowering the daily dose of the estrogenic component (basically, ethinyl estradiol) has beneficial effects, this is not really the case with the progestational component where a variety of agents are utilized today and where the biological activity, rather than the mass, is the discriminating factor. Today, two new progestins – dienogest and drospirenone – are administered in milligram daily doses (namely more than ten-times the dosage of other marketed progestational compounds).

> "...a number of innovations are being applied to hormonal contraception: the first is a multiplicity of ways of administration."

At present, a number of innovations are being applied to hormonal contraception: the first is a multiplicity of ways of administration. Besides the oral and intramuscular routes, the subcutaneous, intrauterine, intravaginal, transdermal and even intranasal routes have been adopted or are being investigated. Products utilized in hormonal contraception today have a duration of action ranging from 1 day to 5 years; they are based on the administration of either an estrogen–progestin combination or progestin alone; their mechanism of action involves either ovulation inhibition or a peripheral effect. In addition, even for combined oral contraception, new regimens have been introduced to reduce the number of bleeding episodes from 13 to four, or even one per year [7].

In this Special Focus issue, a number of specialists will discuss the current situation in hormonal contraception, starting with an overview of currently available pills, our present knowledge of risks and side effects, as well as of benefits, including non-contraceptive ones. Several specific issues will be addressed, such as effective treatment of heavy bleeding and the age-old problem of risk of venous thromboembolism.

On the social front, women's expectations when opting for hormonal contraception – and how these changed over time – will be summarized; in addition, patterns of use and the somewhat controversial topic of over-the-counter distribution, will be debated.

We hope that this overview, albeit partial, will be useful to those who wish to approach hormonal contraception in a rational and modern way.

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