Benefits and Risks of HORMONAL CONTRACEPTION

Has the Attitude Changed?

Edited by A.A. Haspels and R. Rolland

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Chairman's Introduction

A. A. Haspels

It is with pleasure that I welcome you, on behalf of Professor Rolland and myself, to Amsterdam for this International Symposium on 'Benefits and Risks of Hormonal Contraception'.

As a means of family planning the pill is about 25 years old – a timespan which has been characterized by an enormous increase in public interest and concern with family health and family-planning.

Undoubtedly we have learned a lot over the last 25 years. As you see in Figure 1, in the seventies in Holland relatively more fertile women used the pill than in any other country in the world.

In 1974 new combination pills were introduced containing less than 50 μg of ethinyl estradiol. In 1981 50% of Dutch pill-users took a sub-50 (Figure 2). The same is true for the Scandinavian countries.

In our own University Clinic 95% of pill-users take a sub-50 pill; only 5% use a 50 μg pill on medical indication. This decrease in estrogen dosage, which is usually accompanied by a decrease of progestational component as well, has resulted in a decrease of thromboembolic disease.

Factors that are still important to consider are diabetes mellitus, hypertension, adipositas and smoking.

Good selection of patients together with the prescribing where possible of sub-50 pills may result in the numbers of complications and side-effects being close to those encountered in the control group.

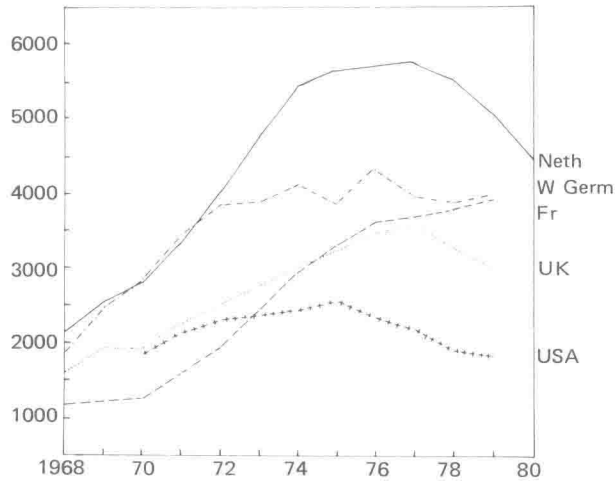

Figure 1 Number of pill-packs per 1000 fertile women aged 15–45

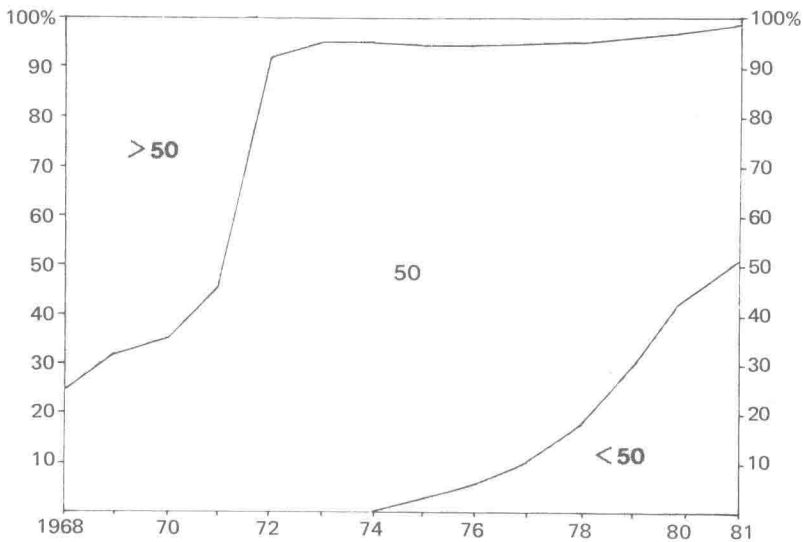

Figure 2 Combination pills – percentage with sub-50 μg estrogens

Most of the speakers today are actively engaged in contraceptive research and, from reading over their papers, it becomes clear that they have placed their work in the broader context of present day knowledge. It remains for me to mention how indebted we are to Schering, whose financial help made it possible to mount a conference of this quality!

Opening Remarks

H. Hannse

I have the pleasure of welcoming you on behalf of my colleagues from Schering AG to this international symposium. We appreciate it highly that you accepted our invitation to this meeting, sacrificing some of your precious time. I hope you will not be disappointed leaving this room tonight and not regret having come here.

Almost exactly 21 years ago our company, Schering AG, introduced the ovulation inhibitor Anovlar^{R} in Australia. Anovlar represented the first hormone preparation to be developed in Europe especially for contraception. In the following 21 years a number of other hormonal contraceptives have been developed, ten of them alone by Schering AG. What kind of progress has this development produced and where are we today? The intention of this symposium is to give us a general picture of the accumulated experiences of more than two decades of research and development. I wish to thank in advance the moderators and speakers who are prepared to make a contribution to this symposium from the point of view of their special area. I am especially grateful that Professor Haspels and Professor Rolland have been willing to act as chairmen of this meeting. The 'Father of the Pill' is correctly deemed to be the American reproduction physiologist, Dr Gregory Pincus, who, together with the gynecologists Rock and Garcia, tested the principle of hormonal inhibition of ovulation in the years

1951–1958 and demonstrated its practicality with nearly 100% reliability in preventing conception.

The scientists of our company based their work on this experience when they developed Anovlar, using an highly effective progestogen synthesized in Berlin. If Schering AG was able to play the role of a pioneer in the realization of what was at the time a new biological principle for contraception, it was because Schering's researchers had already created important preconditions for doing so in the 1920s and 1930s. I include amongst these preconditions the investigation of the cybernetic mechanism of control in the endocrine system that makes it possible to prevent ovulation with progestogen–estrogen combinations. Members of our research departments like Hohlweg and Junkmann made a decisive contribution to the elucidation of this feedback mechanism.

After their isolation and purification, the structure of the female sexual hormones was explored and demonstrated by synthesis in cooperation with Schering AG by Professor Butenandt of Göttingen. The isolation of estrone succeeded in 1929 and that of progesterone in 1934. Butenandt was awarded the Nobel prize for these achievements in 1939. This advance made possible the large scale semisynthetic production of female hormones and their broad therapeutic use in the form of preparations like Progynon^{R} and Proluton^{R}. Concentrates and extracts made of biological material used until then could be replaced by exactly dosed preparations with constant efficacy.

In 1938, in our central laboratory at that time, Inhoffen and Hohlweg synthesized ethinyl estradiol that turned out to be a highly potent and, above all, orally effective estrogen and is still today the most important estrogen component of oral contraceptives worldwide. In the same year ethinyl testosterone, also called ethisterone, was synthesized. It is the parent substance of many ethinyl compounds of the 19-nor series which include the most important progestogen components of oral contraceptives used today. Norethisterone was the first to be synthesized by

Djerassi in 1951. Schering in Berlin took the step of creating norethisterone acetate, the progestogenic effect of which is clearly stronger than that of the basic substance. A decisive advance was the total synthesis of norgestrel by Hershel-Smith in 1961. Norgestrel is an enanthiomeric mixture of two components. With the help of microbiological methods and stereoselective chemical synthesis Schering succeeded in producing the pure levonorgestrel, the biologically effective component of this mixture which constitutes norgestrel. Today in hormonal contraception levonorgestrel is the most widely used oral progestogen.

Further contributions made by our company, Schering AG, to the development of fertility control were the so-called calendar packs which made the control of the daily intake of the pill much easier for women. The first pack with 21 coated tablets and the imprinted names of the individual days of the week was introduced in 1963 for application according to the plan '3 weeks on, one week off'. In 1964 there followed a pack with 28 coated tablets in the case of which the medication-free interval was bridged with seven placebos in order to avoid mistakes when starting a new pack after the break. In 1973 it was possible to introduce Microgynon^{R} 30 as the first preparation with only 30 μg of EE per coated tablet, that is still today the lowest dose of the estrogen component in birth control pills. In our view the present ultimate in the optimization of hormonal contraceptives is represented by Triquilar^{R}, in which it was possible to reduce the total amount of sexual steroids required per cycle to a minimum, namely only 2.6 mg, while maintaining a reliable contraceptive effect! If you keep in mind that it started with 200 mg per cycle in the case of the Pincus preparation, that clearly shows what progress has been achieved in the last two decades.

After my opening remarks, let us learn how the balance of benefits and risks of hormonal contraception more than two decades after the introduction in the daily practice of medicine is

judged by leading international experts. I open this symposium officially and pass the word to the moderator of the first session, Professor Breckwoldt!

Company Note
Triquilar[R] the triphasic pill developed by Schering is clinically proven in more than 20 000 documented cycles and in far more than 16 million user cycles in the short time since its availability. Other trade names are Trigynon[R], Logynon[R], Trionetta[R], Triagynon[R] and Trikvilar[R].

Contents

Section I

The Present Situation in General

Moderator: M. Breckwoldt

Chapter 1

What does it take to develop a new contraceptive?

E. Diczfalusy

Do we really need improved and new fertility regulating agents? This problem is debated mainly in the Western world, sometimes perhaps at a pleasant distance from reality. However, in developing countries the views are different and Vice Prime Minister Chen Mu-hua of the People's Republic of China[1] and Prime Minister Indira Gandhi[2], two ladies representing more than 40% of the population of the world, repeatedly urged intensified international efforts (especially through the services of the World Health Organization) to develop a large variety of safe and inexpensive fertility regulating agents.

Why do we need such a large variety of methods? Because – due to cultural, socio-economic and religious differences – certain methods are unacceptable to certain populations. Furthermore, different methods are needed for different age groups. Differences in the development of the health services represent another important reason. Moreover, the frequency of side-effects varies in different populations. Unexpected effects might be observed following long-term use of any method, and – because of the polymorphism of human populations – rare adverse effects may occur in a few specially sensitive individuals, using almost any method.

If there is such a great need for new methods, why don't we develop a large variety of them at once? Indeed, when the first oral contraceptive, Enovid^{R}, was developed, it took only some