# The 2nd International Norgestrel Symposium

# The second international norgestrel symposium

## Some metabolic considerations of oral contraceptive usage

*Proceedings of the 1974 Symposium held at The Royal College of Physicians, London, England*

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# Welcome

**Sir John Peel**

*Chairman, Board of Science and Education, British Medical Association, London, United Kingdom*

Professor Fairweather, ladies and gentlemen, my first task is to welcome you all to this important symposium. For myself, I was very greatly honoured and appreciate the invitation to preside over this symposium as I had the privilege of doing the same thing some five years ago when the first Wyeth symposium on norgestrel was held in this hall in 1968. I should like to take this opportunity of congratulating and thanking John Wyeth & Brothers Ltd. who, through the agency of their Department of Postgraduate Education, and with the close collaboration of Excerpta Medica, have had the initiative and the imagination to bring together such a distinguished number of scientists and clinicians from many parts of the world to present their experiences and the results of their researches into the problems of oral contraception in general and norgestrel in particular. As a representative of the host country, I am sure you would wish me to extend a very warm welcome to all our overseas visitors who have travelled such long distances in many cases to be with us today. From a personal point of view I should like to express my particular thanks to Mr Patterson and Dr Johnson of Wyeth and to Mr Cauverien and Mrs Sharp of Excerpta Medica for all the personal trouble that they have taken in organising this meeting.

Now, when the first Wyeth symposium was held in 1968, norgestrel was presented at that time, after six years of intensive biological investigation, as a new synthetic progestogen qualitatively similar to progesterone but more potent and highly effective when given by mouth. Today I am told that something like 50% of the world users of oral contraception are using a preparation which contains norgestrel. Its potent estrogenic antagonism made it a preparation of the utmost importance, especially at a time when the possible dangers and complications of the estrogenic content of oral contraceptives were being given perhaps overmuch and the wrong sort of publicity with consequent rejection of oral contraception by some sections of the public. To many of us it does seem difficult to understand the relatively slow, and I say 'relatively' deliberately, acceptance of oral contraception when one considers its remarkable efficiency. The public in many parts of the world seem quite happy to smoke themselves to death, to drug themselves to death, to drink themselves to death, with total abandon, but when there is the slightest possible threat to their reproductive or sexual functions, however remote, this raises emotional barriers which defy reason and common sense.

Nonetheless oral contraception is now progressing very, very rapidly and we hope that the recent publication from the Royal College of General Practitioners will do much to allay anxieties in the public as well as to inform the profession. Nevertheless, the side effects and the complications are a reality and, quite rightly, large sums of money are being poured into scientific and clinical research with a view to minimising these risks without impairing the efficiency of any of the preparations. But it is only by intensive research and clinical evaluation and follow up that it is possible to assess the significance of the minor,

but nonetheless definite, effects upon the cardiovascular system, the endocrine glands and metabolism to mention but some. The results of some of these researches will be presented to us today. We shall be able to see how much further we have gone during the last five years in developing new combinations, long-acting preparations, and other lines of progress which will be to the great advantage of the users in a great many parts of the world and in different types of population. Furthermore, it is only by the ever increasing and most careful selection of the most suitable preparation to prescribe in individual patients that we are going to get the best results. Doctors have a vitally important role to play and the blunderbuss prescription of 'the pill' without reference to proper medical, gynaecological family and social history taking, or examination, will so frequently lead to some of these complications which a greater degree of individualisation in prescribing would have avoided. The sort of detailed scientific and clinical facts about oral contraception which I am sure will emerge today, will be one more contribution to the ever growing encyclopaedia of knowledge which must be made known to the medical profession and, through them, to their patients.

These proceedings are to be published thanks to Excerpta Medica and I am sure that we shall all want to receive this volume in due course and study the details that will perhaps flash across our minds and on the screen rather rapidly today. Now Professor Fairweather is going to look after this meeting as symposium chairman and Professor Morris is going to have the difficult task at the end of the day of summing up in five minutes what everybody has said. We are very grateful to them both for what I know is going to be an arduous task, and so, without more ado, I will hand the meeting over to Professor Fairweather. Thank you very much indeed.

# Introduction

**D.V.I. Fairweather**

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It is a pleasure to act as symposium chairman and to undertake, in due course, the editorship of the proceedings of the symposium.

As Sir John Peel has mentioned, the first Wyeth Symposium was held at the Royal College of Physicians in 1968. Since that time we know that a combination of norgestrel and ethinylestradiol has been found widely acceptable for prescription by doctors throughout the world. We meet today to hear of developments that have taken place in the interim years.

Much attention has been paid by the medical profession to the long-term effects of hormonal contraception. Indeed, I would venture to say that no other group of medical compounds has been so thoroughly tested nor the results of their usage (short- and long-term) scrutinised in such detail.

The symposium, coming so closely in time to the recent publication of the results of a large prospective study of contraception in this country, will hopefully add to knowledge in the many important aspects of fertility control. Again we look forward to practical suggestions from an experienced panel, for surely the practising physician can play an important role in making maximum use of the tools we have to tackle the world population problem.

Finally, for the sake of all of us, it seems appropriate to say a word on the progestin being discussed today. It represents an original anti-estrogenic progestin which does not metabolise to estrogen. The original compound was a racemic mixture composed of d and l isomers. Subsequent chemical separation permitted the use of the active d-form, since it had been shown that no biological activity resided in the l-form.

The first norgestrel conference mainly dealt with clinical experience of the combination of 500 $\mu$g dl-norgestrel + 50 $\mu$g ethinylestradiol, but it is anticipated that newer combinations and the results of their use will be presented today.

With anticipation of a productive conference, I call on the first speaker.

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SESSION IV - *Advances and developments of norgestrel-containing contraceptives*

# International aspects of the use of norgestrel

**E. T. Tyler***

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*The author, who conducted the first United States trials on oral contraceptives starting in 1956 shortly after the first studies had begun in Puerto Rico, has been involved in comprehensive investigations of hormonal contraception for about two decades. This report analyzes the growth of world-wide use of birth control pills as correlated with increasing studies of the actions of various pills as well as reductions in amounts of hormonal ingredients. This report covers personal observations noted in many different countries as well as a review of statistical data available regarding use in various areas.*

*In general terms, excellent efficacy has been the recognized feature of the use of oral contraceptives, but acceptance in many countries has been contingent upon adequate demonstration of long-term safety and minimal side effects. The continued long-term controlled studies in clinics similar to the author's as well as the development of low-dosage forms, such as those represented by norgestrel, have been the major factors that have introduced this form of contraception - in some cases the only form of contraception - in many countries of the world.*

In 1956, when the first United States studies of oral contraceptives were begun at the Family Planning Centers of Greater Los Angeles, there was considerable skepticism in the scientific world about the potential for widespread usefulness of this startling new family planning innovation. Although there was some encouraging information from the then recently initiated Puerto Rican study (1), it was seriously questioned whether hormonal medications could be safely and effectively used. As a matter of fact, many endocrinologists, including this author, were skeptical about the contraceptive use of potent agents, and at the 1958 American Medical Association meeting, in one of our first reports (2), after about 2 years of study, we made the following comments:

> 'The use of progestational steroids for conception control purposes provides a potentially relatively simple form of family planning. On the other hand, it also initiates for the first time the use of anti-fertility measures which can theoretically have constitutional actions. Until now the conception control measures used have been medications or devices which, as far as we know, do not possess other than local

* Medical Director of Family Planning Centers of Los Angeles and Past President of International Family Planning Research Association and American Association of Planned Parenthood Physicians.

effects. Oral conception control, on the other hand, takes advantage of the fact that one of the normal physiological functions requisites for reproduction can be altered. The particular oral method used in this study has, as its basis, interference with the cycle of activities which ordinarily takes place to provide an ovum available for fertilization'.

'Because information about possible harmful results from long-term suppression of pituitary function is lacking, it must be acknowledged that the use of these compounds should be carefully supervised until such data are accumulated . . . The estrogenicity of the effective compounds further emphasizes the need for carefully observing these patients for possible deleterious effects caused by hormonal stimulation over long periods of time. Hence, we conclude that while there is substantial evidence of effectiveness there is still much to be known, particularly in relation to long-term safe use in the field of conception control'.

Perhaps this represented undue caution, but as information has developed in the intervening two decades, it appears fairly definite that a few serious side effects can occur in an extremely small percentage of women. This has been reflected in various warnings regarding prescribing oral contraceptives required by government agencies in several countries.

Despite the serious problems that have arisen, some of which have been etiologically only theoretical and a few probably actual, the use of birth control pills has gained widespread international acceptance. While their availability has not yet resolved the population crisis, it is obvious that this form of birth control is having substantial impact in many parts of the world.

There are undoubtedly several reasons why oral contraception has become such an acceptable and useful form of family planning during the past two decades. A major one is the obvious fact that continuing usage, particularly among those conducting long-term toxicity studies, has provided a certain degree of reassurance as to the general safety of birth control pills for the vast majority of women using them (3,4). I can recall that at the International Planned Parenthood Congress held in New Delhi in 1958, delegates from several of the developing countries were reluctant to institute even small pilot programs of oral contraception in their family planning units because they wanted to see 'complete' evidence concerning safety. They looked to studies in places like the United States and England to reassure them, and did not want to 'experiment' on their own peoples. This has been an unfortunate situation, since in many developing countries the trauma caused by unwanted pregnancies and an unbridled population growth has been far greater during the years of availability and non-use of oral contraceptives than might have been anticipated from occurrence of serious side effects on the basis of statistical data currently available.

Although this discussion concerns the international aspects of oral contraception, we should probably briefly review the types of contraceptives we are discussing, along with some general impressions of their mechanisms of action. The initial impetus to the utilization of hormones in conception control resulted from the established fact that peripheral ovarian hormones, such as the estrogens, when administered exogenously, could inhibit ovulation. Although it had been known for several years that estrogens, as well as certain synthetic progestogens in large doses, could inhibit ovulation, it was not until the development of the 19-norsteroids and their recognition as far more clinically potent progestogens than anything previously available, that it became apparent to the group of original Puerto Rico investigators (including one of the members of this Symposium, Dr. Garcia) that ovulation could be prevented while the endometrium was maintained in an intact condition. In the early 1950's (4), I utilized one of the 19-norsteroids, norethisterone (norethindrone) in the luteal phase of the cycle in order to increase the development of the endometrium in infertility, and found that this chemical was many times more potent than

previously available ethisterone (6). It had marked effects on the BTB and could substantially delay menses. When the group in Puerto Rico began using the norethynodrel-mestranol combination in doses of 10 mg and 1.5 mg, respectively, as a contraceptive, we initiated the first norethindrone study utilizing doses of 10 mg norethindrone with 0.06 mg mestranol. It was apparent from the beginning that there were probably three contraceptive modes of action attributable to these preparations: (a) inhibition of ovulation, with (b) alteration of cervical mucus causing it to become impenetrable to sperm, and (c) distortion of the endometrium, presumably making it unsuitable for implantation. There are also other conjectured mechanisms, such as changes in tubal motility, uterine contractions and possibly elimination of capacitation.

After a few years of increasing studies of the effectiveness of the combined medications, trials of 'sequential' hormonal contraceptives were begun, in which estrogen alone was employed for two weeks of the therapy interval and the combination of estrogen and progestogen for only one week. It was soon demonstrated that sequential contraception was similarly effective, although perhaps not quite to the same degree as the combined (7). But I think the critical date here is 1966, when we, and I'm sure others, perhaps before us started the initial norgestrel combination studies and soon found out that this particular progestogen was remarkable in that the dosage levels were so far lower than anything previously used, that we had reached a point where perhaps even the very skeptical physician could feel that he could use a compound in a very minimal dose and still get the kind of effectiveness we were getting from the higher doses (8). And I think this represented a marked step forward in our development of international use of oral contraceptives. There are indications in recent studies of ours and others that even a lower dose norgestrel combined tablet (with only 0.150 mg d-norgestrel) will probably soon be available.

In addition to the combined and sequential contraceptives we have, during the past several years, witnessed the development of the so-called 'mini-pill'. This very low-dose progestogen is given alone on a daily basis with no estrogen. In the case of norgestrel the amount employed in the United States is 0.075 mg dl - a very small dose indeed - or 0.030 mg d-norgestrel outside the United States (10). While the mini-pill does not provide the same degree of effectiveness as either combined or sequential pills, and is at times associated with unacceptable amounts of bleeding irregularity and related difficulties, it has achieved a place in oral contraception in specific types of cases where estrogen use is not desirable. In general terms, it may be stated that combined contraceptives (when properly used) are associated with pregnancy rates of about 0.5, while mini-pills are in the less effective range of 3 to 4 (8-13).

Studies suggest that the mini-pill usually does not inhibit ovulation, but rather that contraceptive effectiveness is due to endometrial alterations and probably changes in tubal function. In addition, the progestogen alters the cervical mucus so that at the time of ovulation it is impenetrable to sperm (11-15).

Those physicians who have had long experience with oral contraceptives usually choose low-dose combined agents, such as norgestrel-ethinylestradiol, for the majority of patients and reserve the mini-pill for those where estrogen is contra-indicated or undesired. In this connection it must be emphasized that, while the serious problems, such as thrombophlebitis, that have been reported to be caused by oral contraceptives are believed to be estrogen-related (assuming that there is an etiological relationship), manufacturers of estrogen-free mini-pills in the United States are required to insert the same precautionary warnings in the package inserts as are required for the combined pills. Thus, the advantages presumably obtained by the elimination of estrogen are not accepted as completely definite by the United States Food and Drug Administration, a situation which is confusing in view of the many efforts that research and government agencies have made to obtain reduction or elimination of the estrogen content in birth control pills. It may be hoped that this contradictory situation can be resolved when more data are accumulated on the comparative incidence of side effects with mini-pills, low-estrogen pills, and com-

bined pills.

Although pioneering work on oral contraceptives was done in Puerto Rico, the United States, and England, it should be noted that our present total information concerning oral contraceptives - their acceptability, pharmacology, and possible toxicity - has been a product of the individual efforts of many leading scientists internationally, working on their own special research programs. Excellent research in many diverse countries has not only increased available knowledge about oral contraception, but also has promoted generally increased interest in birth control in the particular areas where the studies were done.

In Mexico, for example, intensive investigations by such prominent researchers as Rice-Wray (16), Martinez-Manautou (17), Zaldivar (18), and others (19-21), helped to make the use of oral contraceptives a popular form of family planning. As a matter of fact, we owe the concept and discovery of progestogen-only mini-pills by continuous administration to a Mexican investigator (17). In Peru, Kesseru and Larrañaga have studied in detail alterations in cervical mucus brought about by various contraceptives as correlated with sperm migration (14). These investigators have designed detailed *in vitro* studies to help differentiate the varying degrees of alterations in sperm migration produced by different progestogens at varying doses (15). They have also been able to demonstrate contraceptive effectiveness of the very low-dose norgestrel tablets and have developed a method for the post-coital administration of d-norgestrel which has a high degree of efficacy (22). Some of the pharmacological studies of the effects of low-dose norgestrel preparations were conducted by Larsson-Cohn, Johannsson, and Gemzell in Sweden (23).

Attempts have been made to determine acceptability and usefulness of low-dose oral norgestrel and other hormonal methods in a number of countries. There have been significant studies by Briggs and Briggs in Zambia (24), Sai in Ghana (25), Chinnatamby in Sri Lanka (26), Apelo and Veloso in the Philippines (27), Coutinho in Brazil (28,29), Gun, Kindu and Poddar in India (30), and Villedieu in France (31).

In addition, there has been a wealth of recent research including new formulations in Argentina, Belgium, Brazil, France and the U. K., the results of which are being presented in this volume.

The result of all of this investigation has led to at least one definite conclusion: oral or other hormonal contraception is extremely effective and is generally accepted by populations where it is properly offered. In addition, there have been enough studies conducted to cast some doubts on the *complete* safety of these agents, and no serious student of hormonal contraception denies at least a *possible* relationship of oral contraception to such serious problems as thrombo-embolism. On the other hand, there is still real doubt as to whether the *presently available* s.- .stical evidence *proves* an etiological relationship between the pills and vascular disease (32). The same controversy concerns changes in liver function, carbohydrate metabolism, eye pathology, and other side effects. These disturbing questions have tended, in some countries, to neutralize the voluminous evidence demonstrating the usual safety, effectiveness and general usefulness of oral contraceptives with the result that their use in some areas lags far behind others.

In the so-called developed countries oral contraceptives play a dominant role in family planning programs through private practice, community organizations and governmental agencies. We have made an effort to determine some specific information as to usage of oral contraceptives in the various countries, and the latest figures available are summarized in Table 1 and Table 2 (33). In addition, to determine the impact of low-dose contraceptives on prescribing of birth control combination agents, it should suffice to state that in 1969 norgestrel-based products comprised over 15% of oral contraceptive usage in 19 countries, including the United States. In 1973, for these same countries, norgestrel preparations comprised 35% of the oral contraceptive usage. This is probably an indication of a general tendency to prescribe the lower dose combinations.

In summary, there are four points I would like to emphasize:

**Table 1** Retail pharmacy purchases of oral contraceptives in thousands of cycles in selected areas by country and year, 1964-1972*

| | 1964 | 1966 | 1968 | 1969 | 1970 | 1971 | 1972 |
|---|---|---|---|---|---|---|---|
| **Developed areas** (including Europe) | | | | | | | |
| Australia | | | | 7,380.2 | 6,815.7 | 8,191.3 | 8,976.5 |
| Austria | | | 1,285.1 | 1,794.9 | 2,174.1 | 2,671.2 | 3,332.0 |
| Belgium | | | 2,525.1 | 2,541.1 | 2,996.0 | 3,464.6 | 3,909.8 |
| Canada | 2,135.0 | 6,567.0 | 9,641.0 | 11,650.0 | 14,012.0 | 15,889.0 | 17,117.0 |
| Finland | | | 1,289.9 | 1,838.0 | 1,610.7 | 1,782.2 | 1,865.9 |
| France | 324.4 | 1,381.0 | 5,911.9 | 7,405.9 | 8,231.0 | 11,833.9 | 15,299.0 |
| Germany, West | 2,375.0 | 5,254.6 | 18,653.4 | 24,850.8 | 29,369.9 | 37,879.1 | 42,901.1 |
| Greece | | | 157.7 | 235.3 | 226.9 | 277.1 | 286.9 |
| Ireland** | | | 174.0 | 202.2 | 151.5 | 228.8 | 334.4 |
| Italy | 91.6 | 594.0 | 1,100.3 | 1,893.7 | 1,808.8 | 2,231.2 | 3,677.4 |
| Japan** | | 3.2 | 465.8 | 1,613.4 | 1,042.4 | 1,368.2 | 1,911.9 |
| The Netherlands | | | 4,013.1 | 5,194.0 | 6,518.0 | 7,760.0 | 10,149.6 |
| New Zealand | | | | 1,629.4 | 1,593.6 | 1,896.6 | 1,949.8 |
| Spain | | | 1,648.7 | 1,898.4 | 1,823.4 | 2,285.0 | 2,760.0 |
| United Kingdom | 2,641.0 | 6,854.0 | 11,457.5 | 14,027.5 | 13,824.7 | 16,997.9 | 18,948.2 |
| United States | 31,846.3 | 65,340.8 | 78,009.6 | 75,469.2 | 70,655.3 | 81,203.7 | 89,147.2 |
| Yugoslavia | | | 1,439.3 | 1,527.5 | 1,775.6 | 2,059.8 | 2,550.8 |
| Subtotal | 39,413.3 | 85,994.6 | 137,772.4 | 161,151.5 | 164,629.6 | 198,019.6 | 225,117.5 |
| **Developing areas** | | | | | | | |
| Asia | | | | | | | |
| Iran | | | | | | | 596.8 |
| Lebanon | | | | | | | 247.9 |
| Philippines | | | 746.1 | 900.9 | 932.9 | 755.2 | 623.0 |
| Turkey | | | 841.0 | 1,058.2 | 932.1 | 1,349.5 | 1,484.4 |
| Subtotal Asia | | | 1,587.1 | 1,959.1 | 1,915.0 | 2,104.7 | 2,952.1 |
| Latin America | | | | | | | |
| Argentina | | | 3,152.3 | 3,008.0 | 3,406.0 | 3,514.3 | 3,924.3 |
| Brazil | | | 7,040.6 | 9,914.0 | 6,895.0 | 12,157.4 | 10,383.2 |
| Central America | | | | | | | 1,012.8 |
| Colombia | | | | 1,122.0 | 1,105.0 | 1,404.2 | 1,641.5 |
| Mexico | | | 2,145.6 | 2,648.6 | 2,810.0 | 2,715.8 | 3,628.4 |
| Peru | | (1967) | 385.6 | | 376.0 | 497.6 | 680.3 |
| Puerto Rico | | | 246.0 | 321.0 | 233.0 | 311.0 | 427.0 |
| Venezuela | | | 501.7 | 551.0 | 533.0 | 716.1 | 528.4 |
| Subtotal Latin America | | | 13,471.8 | 17,564.6 | 15,378.0 | 21,316.4 | 22,525.9 |
| Subtotal Developing areas | | | 15,058.9 | 19,523.7 | 17,293.0 | 23,421.1 | 25,478.0 |
| *Total* | | | *152,831.3* | *180,675.2* | *181,922.6* | *221,440.7* | *250,595.5* |

* These figures do not include usage in hospitals, family planning clinics, or samples.
** Figures are probably low since usage in meaningful numbers does not normally occur until age 18.

**Table 2** Minimum percentage of women aged 15-44 supplied with oral contraceptives through commercial channels in selected areas, 1964-1972

| | 1964 | 1966 | 1968 | 1969 | 1970 | 1971 | 1972 |
|---|---|---|---|---|---|---|---|
| **Developed areas** (including Europe) | | | | | | | |
| Australia | | | | 22.7% | 20.2% | 24.2% | 25.6% |
| Austria | | | 6.9% | 9.7% | 11.7% | 14.7% | 17.7% |
| Belgium | | | 10.1% | 10.2% | 12.0% | 14.0% | 15.4% |
| Canada | 4.2% | 12.2% | 16.9% | 19.9% | 24.0% | 26.6% | 28.0% |
| Finland | | | 9.5% | 13.5% | 11.9% | 13.1% | 13.5% |
| France | 0.3% | 1.1% | 4.5% | 5.6% | 6.3% | 8.8% | 11.3% |
| Germany, West | 1.5% | 3.4% | 12.3% | 15.5% | 17.9% | 22.8% | 25.8% |
| Greece | | | 0.6% | 0.9% | 0.9% | 1.0% | 1.1% |
| Ireland* | | | 2.5% | 2.9% | 2.2% | 3.2% | 4.8% |
| Italy | 0.1% | 0.4% | 0.7% | 1.2% | 1.2% | 1.5% | 2.4% |
| Japan* | | | 0.1% | 0.5% | 0.3% | 0.4% | 0.6% |
| The Netherlands | | | 11.9% | 15.4% | 19.3% | 22.1% | 28.9% |
| New Zealand | | | | 21.0% | 21.1% | 24.3% | 24.2% |
| Spain | | | 1.8% | 2.1% | 1.9% | 2.4% | 3.0% |
| United Kingdom | 1.9% | 4.9% | 8.2% | 10.1% | 9.9% | 12.2% | 13.6% |
| United States | 6.4% | 12.7% | 15.6% | 14.9% | 13.0% | 14.9% | 16.2% |
| Yugoslavia | | | 2.4% | 2.5% | 2.8% | 3.3% | 4.0% |
| **Developing areas** | | | | | | | |
| Asia | | | | | | | |
| Iran | | | | | | | 0.8% |
| Lebanon | | | | | | | |
| Philippines | | | 0.8% | 0.9% | 1.0% | 0.7% | 0.5% |
| Turkey | | | 0.9% | 1.1% | 1.0% | 1.4% | 1.5% |
| Latin America (including Puerto Rico) | | | | | | | |
| Argentina | | | 4.6% | 4.3% | 4.8% | 5.0% | 5.5% |
| Brazil | | | 3.6% | 4.1% | 2.7% | 4.7% | 4.0% |
| Colombia | | | | 0.7% | 1.0% | 0.5% | 1.1% |
| Mexico | | (1967) | 1.2% | 2.1% | 2.1% | 2.1% | 2.6% |
| Peru | | | | | 1.2% | 1.4% | 1.9% |
| Puerto Rico | | | 3.2% | 4.1% | 2.7% | 3.6% | 4.7% |
| Venezuela | | | 2.0% | 2.2% | 2.0% | 2.6% | 2.9% |

* Figures are probably low since usage in meaningful numbers does not normally occur until age 18.

1. We have very effective hormonal contraception available in many countries in various forms, and widespread international use and acceptance. Further educational efforts are required.
2. There are still several questions to be answered about side effects and long-term problems.
3. Progestogen doses in present combined pills are in the range of 1/40th of the original oral contraceptive dose.
4. As effective hormonal doses are lowered, there is a tendency toward prescribing these newer low-dose pills rather than those previously employed.

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