COMBINED ESTROGEN–PROGESTOGEN CONTRACEPTIVES

These substances were considered by a previous Working Group, in June 1998 (IARC, 1999), under the title 'Oral contraceptives, combined'. Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Introduction

Combined hormonal contraceptives consist of an estrogen and a progestogen, and act primarily by preventing ovulation through the inhibition of follicle-stimulating hormone and luteinizing hormone. The progestogen component also renders the cervical mucus relatively impenetrable to sperm and reduces the receptivity of the endometrium to implantation. These mechanisms render combined hormonal contraceptives very effective in the prevention of pregnancy. Annual failure rates vary between 0.02% (two per 10 000 women/year) when full adherence to instructions for use is assumed (Ketting, 1988) and 5% for typical use (Fu *et al.*, 1999).

A variety of innovations have been developed since combined hormonal contraceptives were first made available in the late 1950s, but not all of these have proved valuable in practice. Changes in drug components, doses used and the temporal sequencing of exposure to drugs have incorporated new technologies and responded to suggested risks. While regional variations in use are abundant, the dominant trends have been towards less androgenic progestogens, lower doses of estrogen and progestogen, the near abandonment of hormonal contraceptives with an estrogen-only phase, a proliferation of different product formulations and the continuing development of novel delivery systems.

In combined hormonal contraception, ethinylestradiol is the most common estrogen, although other are used occasionally. A variety of progestogens is available and these differ in their properties with regard to progestogenic and androgenic characteristics. The estrogen and progestogen contained in combined hormonal contraceptives are usually given in a monthly cycle, and a variety of regimens ensure that the doses of the two constituents

produce menstrual cycling. In general, estrogen and progestogen are taken in combination for 21 days followed by 7 drug-free days (often placebo tablets) during which time withdrawal bleeding usually occurs. Other cyclic schedules may be used to reduce or eliminate menses. A constant combination of estrogen and progestogen doses may be used (monophasic) or the doses of progestogen and (less often) estrogen may vary in two (biphasic) or three (triphasic) phases. While oral administration predominates, combined hormonal contraceptives can also be administered by injection, a transdermal patch or a transvaginal device.

Although the primary indication of these medications is to prevent pregnancy through regular use, they are also used to regulate menstrual disorders, to treat acne vulgaris or for emergency contraception. Worldwide, more than 100 million women use combined hormonal contraceptives. While their use is more common in developed countries, substantial consumption also occurs in the developing world. Recent trends suggest that overall use has continued to increase slowly in some regions, while it has remained constant in others. The demographic and social characteristics of combined hormonal contraception users are known to differ from those of non-users of these drugs.

1.2 Historical overview

Researchers in the late nineteenth century noted that follicular development and ovulation were suppressed during pregnancy and that extracts of the corpus luteum inhibited ovulation in laboratory animals. In 1921, Ludwig Haberlandt proposed that similar extracts might act as a contraceptive (IARC, 1999; Fraser, 2000).

Three estrogens were identified in the late 1920s and 1930s — estrone, estriol and estradiol. Progesterone was identified in 1929 and was crystallized in 1934. An oral equivalent of progesterone was not available until 1941, when diosgenin was synthesized from extracts of the Mexican yam. Further experimentation yielded the synthesis of norethisterone (known as norethindrone in the USA) in 1951 and norethynodrel in 1952. These compounds were named progestogens (or progestins) due to their progesterone-like properties (IARC, 1999; Fraser, 2000; Junod & Marks, 2002).

In the early 1950s, the combination of estrogen and progestogen was tested as a treatment for infertility, and it was noted that women who took this combined formulation did not ovulate. In 1956, during clinical trials of oral norethynodrel (a progestogen) as a contraceptive, it was found that preparations that contained mestranol (an estrogen) as a contaminant were more effective in suppressing ovulation than those that contained pure norethynodrel. In 1957, the combination of mestranol and norethynodrel was approved for use in the USA for the regulation of menstruation. Even before this combination was approved as a contraceptive in the USA in 1960, it was already being used for such purposes by 0.5 million women. In the same year, it became available in the United Kingdom. Diffusion of this and a second combined hormonal contraceptive formulation (mestranol and norethisterone) to continental Europe and Latin America occurred somewhat later in 1964–68. By the early 1970s, over 25% of women of child-bearing age in many developed

countries were using combined hormonal contraceptives (IARC, 1999; Fraser, 2000; Junod & Marks, 2002; Shampo & Kyle, 2004).

The doses of combined hormonal contraceptives during this early period were 150 μg mestranol and 9.35 mg norethynodrel (Enovid in 1957), but quickly declined to 100 μg mestranol and 2 mg norethisterone (Ortho-Novum in 1964). Doses were further reduced to 50 μg estrogen as confirmation was received that low-dose formulations remained effective with a consequent reduction in adverse effects that had tended to limit continued use. The ease of use, efficacy and reversibility of hormonal contraceptives, as well as changing sexual behaviours and new expectations regarding the regulation of fertility, contributed to the rapid increase in combined hormonal contraceptive use in the 1960s (IARC, 1999; Junod & Marks, 2002).

The upward trend in the use of combined hormonal contraceptives came to a temporary halt in the early 1970s when adverse events associated with their use were highlighted, particularly in women who smoked cigarettes (WHO, 1995). While a variety of side-effects and a risk for thromboembolic events had been recognized earlier, new reports also focused on the risk for cardiovascular disease (Fraser, 2000). As a result, use of combined hormonal contraceptives declined substantially in most developed nations throughout the 1970s. Partly in response to these concerns, a new generation of combined hormonal contraceptives was developed that featured lower doses of estrogen (30 and 35 μg) and newer, more potent progestogens.

Increased use of combined hormonal contraceptives resumed in 1979–81 in many countries, particularly in the light of studies that suggested their relative safety and potential benefits on some outcomes, including reductions in rates of ovarian and endometrial cancer rates (Burkman *et al.*, 2004). At this time, use of combined hormonal contraceptives also increased in many countries in Asia, Africa and the Middle East, facilitated by international aid programmes that were aimed at alleviating the economic consequences of high rates of fertility (IARC, 1999).

At the same time, dose schedules were also modified and refined. With the introduction of biphasic (1982) and triphasic (1984) combined hormonal contraceptives, doses of progestogen were modulated in a manner thought to mimic physiological patterns, although the objective benefits are subject to debate (Van Vliet *et al.*, 2006a,b,c). The previous practice of sequential exposure to estrogen only, followed by combined exposure to estrogen and progestogen, was abandoned after it was found to be associated with an increased risk for endometrial cancer (IARC, 1999).

Further modifications have been made more recently through the continued development of other progestogens, the use of even lower doses of estrogen and the use of alternative dose schedules. Newer progestogens, such as spironolactone-derived drospirenone and more potent and less androgenic gonanes (desogestrel, gestodene), became more common. These formulations were partly aimed at reducing androgenic side-effects such as hirsutism and weight gain. Estrogen doses were reduced to 20 μg and then 15 μg. These low doses may be unsatisfactory for many women because of breakthrough bleeding and they require stricter adherence to instructions for use in order to be effective (Gallo *et al.*,

2004). Other recent innovations in combined hormonal contraception include devices for transvaginal and transdermal administration, variations in length of schedule (both shorter and longer cycles) and combined injectable formulations.

The increase in the use of combined hormonal contraceptives appeared to diminish in the mid-1990s (IMS Health, 2005), possibly due to renewed concerns regarding adverse effects and the growth of alternative contraceptive technologies (e.g. progestogen-only contraception) in developed countries. Similar declining increases in developing countries may reflect a shift towards greater use of other longer-term contraception, including sterilization, injections of progestogen and intrauterine devices (United Nations, 2004a).

In the 1990s, concerns about potential risks of combined hormonal contraceptives for cardiovascular disease (Hannaford *et al.*, 1994) and thromboembolic events persisted. In addition, the risk for breast cancer, which had been a concern since the introduction of hormonal contraceptives, was also re-emphasized (Collaborative Group on Hormonal Factors in Breast Cancer, 1996a,b). Specific concerns were also raised about the increased incidence of thromboembolism associated with progestogens such as gestodene and desogestrel (Jick *et al.*, 1995; WHO, 1995). In spite of these qualms, the effectiveness, ease of use and the risk profile of combined hormonal contraceptives suggest that they will continue to be used to a significant extent in the future. As in the past, the nature of the exposure associated with the components of combined hormonal contraception will probably continue to evolve.

1.3 Preparations of combined hormonal contraceptives

A plethora of products is available for use in combined hormonal contraceptives. Products that are currently available differ in a number of important aspects, including the estrogen compound used and its dose, the progestogen used, the schedule of exposure to the drugs and the route of administration. In addition, identical formulations may carry different brand names in different countries or even within the same country. These products and their ingredients are presented in Annexes 1–3.

The most common estrogen in combined hormonal contraceptives is ethinylestradiol. Over time, other estrogens have been used, including initially mestranol (a pro-drug of ethinylestradiol) and, more recently, estradiol. In the early development of combined hormonal contraceptives, doses of estrogen in the range of 100–150 μg were commonly used. Contemporary combined hormonal contraceptives may be classified by estrogen dose into 'high-dose' (≥ 50 μg), 'moderate-dose' (30–35 μg) and 'low-dose' (15–20 μg).

A variety of progestogens is used in combined hormonal contraceptives. Currently, they are often distinguished as 'first-generation' estranes (such as norethynodrel or norethisterone), 'second-generation' gonanes (such as levonorgestrel or norgestimate), 'third-generation' gonanes (gestodene and desogestrel) and 'fourth-generation' drospirenone. An additional class of progestogens, the pregnanes (e.g. cyproterone and chlormadinone), may also be used. Estranes are highly androgenic, while pregnanes and drospirenone have antiandrogenic activity. The later gonanes are less androgenic than the earlier compounds in

that series. Lower androgenic activity minimizes androgenic side-effects such as acne, hirsutism, nausea and lipid changes. The affinity of individual progestogens for progesterone receptors varies considerably and determines the daily doses required to produce endometrial differentiation. Drospirenone has the lowest affinity (typical daily dose, 3 mg), while the later gonanes have the greatest affinity (0.05–0.15 mg daily dose) (Hammond *et al.*, 2001).

The schedule by which exposure to the drugs occurs may also vary. Most commonly, a constant combination of estrogen and progestogen is used for 3 weeks of a 4-week cycle (monophasic). The doses of progestogen and (less often) estrogen may vary in two (biphasic) or three (triphasic) phases followed by a drug-free phase. While multiphasic schedules seek to mimic physiological variations in exposure to hormones, they may not produce objective benefits over monophasic schedules (Van Vliet *et al.*, 2006a,b). Sequential exposure regimens that used prolonged exposure to estrogen alone are no longer used (IARC, 1999), but a short, 5-day, estrogen-only sequence has been re-introduced. Cycle lengths shorter and longer than 4 weeks may be used with the aim of limiting the duration of menses or eliminating menses altogether (Sulak, 2004). One-day-only use of hormones may be used for emergency contraception.

While oral administration predominates in combined hormonal contraception, the drugs also can be provided by injection, transdermal patch or transvaginal device. Injection of an estrogen and progestogen was used early in the development of hormonal contraception and is still available. Innovations in drug delivery have generated transdermal patches and a vaginal device.

The vast array of products available allows combined hormonal contraception to be tailored to the specific needs and preferences of individual women. While some of the newer products may offer advantages over the older ones, differences in adverse effects and effectiveness are not clear. [In addition, the proliferation of products also represents market differentiation in a large and profitable, but competitive market.]

It is important to recognize that many products are relatively new to the market, particularly those that provide newer progestogens. These, together with products that are currently under development, create a challenge for the evaluation of long-term risk from this class of pharmaceuticals.

1.4 Patterns of use

This section includes the indications of combined hormonal contraceptives, their current prevalence of use globally and trends in the use of these preparations. The characteristics of women who use combined hormonal contraception are also described. Most information on patterns of use of combined hormonal contraceptives is limited to oral forms, and does not include other routes of exposure except for progestogen-only formulations. However, these non-oral forms are generally much less common and information on oral use provides a reasonable proxy for all combined hormonal contraceptive use.

1.4.1 *Prevalence of use*

Based on a compilation of data sources, Blackburn *et al.* (2000) concluded that approximately 100 million women were current users of combined hormonal contraceptives worldwide and, outside of India and China, which have a very low prevalence of use, that 32% of married women in the developing world had ever used them. While variations in their use were enormous, they were the most widely used method of contraception among married women in two-thirds (44/68) of developing countries.

The United Nations (2004b) has compiled data from multiple sources on worldwide patterns of combined hormonal contraceptive use (Table 1). It was estimated that, among women in marital or consensual unions, 7.3% currently use combined hormonal contraception orally and 2.9% currently use hormonal injections or implants. Together, these methods account for 17% of all women who use contraception. Current oral use of combined hormonal contraception is greater in developed nations (15.7%) than in less developed nations (5.8%) (see Table 1), while the converse is true of injectable preparations and implants (0.7% versus 3.3%).

Reported use in the late 1990s varied considerably by region, with a relatively high prevalence of use among women in northern Africa, South-East Asia, South America, North America, New Zealand/Australia and Europe (except eastern Europe) (United Nations, 2004b). On a national level, particularly high prevalences of use were noted in Algeria (44%), Bangladesh (23%), Brazil (21%), Hungary (38%), Iran (21%), Kuwait (29%), Morocco (32%), Thailand (23%) and Zimbabwe (36%). In addition, all countries in western Europe had a prevalence above 30%. In many cases, countries adjacent to those with high prevalence of use had low prevalence: China (2%), India (2%), Peru (7%), Poland (2%), Rwanda (1%), Sudan (5%) and Yemen (4%). A range of factors contribute to these striking differences, including level of economic development, patterns of foreign aid and national family planning programmes (United Nations, 2004c).

Lundberg *et al.* (2004) presented additional information on worldwide variations in use. Current use among women aged 25–44 years varied from < 1 to 58%. In general, the variations within countries were relatively small compared with those between countries. In accordance with other studies, particularly high oral use of combined hormonal contraceptives was noted in western Europe and Australia/New Zealand.

Ross *et al.* (2002) suggested that a hierarchy of preferences for contraceptive methods exists in developing countries and depends on availability of contraception. At the highest level of access, sterilization is generally the method of choice, followed by oral contraceptives, intrauterine devices and condoms in decreasing order of preference. On the contrary, oral contraceptives are the most prevalent method in those countries that have the lowest mean availability of contraception.

Ali and Cleland (2005) also noted substantial variations in oral use of combined hormonal contraceptives within South and Central America where it was fairly prevalent in Brazil and Nicaragua, but low in Peru and Bolivia.

Table 1. Prevalence of oral use of combined hormonal contraceptives worldwide

	No. of women included[a]	Prevalence of oral contraceptive use[b]		Proportion of oral contraceptive use among all forms of contraception (%)[c]	Year of survey
		Mean (%)	Range (%)		
World	1 043 265	7.3		12.1	1998
More developed[d]	170 043	15.7		22.9	1996
Less developed[e]	873 223	5.8		9.8	1998
Africa	117 120	7.3		27.2	1999
Eastern		5.9	1.4–35.5		
Middle		1.6	1.0–16.7		
Northern		17.7	5.1–44.3		
Southern		10.4	5.4–14.7		
Western		2.7	1.8–18.2		
Asia	293 294	4.5		7.1	1997
China		1.7			
India		2.1			
South Central Asia		4.8	0.6–23.0		
South-East Asia		12.8	6.2–23.1		
Western Asia		6.4	1.0–28.8		
Europe	109 277	17.4		26.0	1995
Eastern		6.9	2.3–37.7		
Northern		19.2	3.9–26.0		
Southern		11.8	4.5–21.7		
Western		48.2	30.8–58.6		
Latin America and Caribbean	81 810	13.8		19.5	1997
Caribbean		7.6	2.3–31.5		
Central America		7.5	5.0–18.0		
South America		17.1	3.8–24.5		
USA/Canada	42 029	15.5		20.3	1995
Australia/New Zealand	2 989	23.3		30.7	1998
Oceania (except Australia/ New Zealand)	1 303	4.7	4.4–22.6	17.6	1996

From United Nations (2004b)

[a] Women aged 15–49 in a marital or consensual union (in thousands)

[b] Includes all formulations of oral contraceptives.

[c] Includes oral contraceptives, male and female sterilization, injectable implants, intrauterine devices, condoms, vaginal barriers, other modern methods, rhythm, withdrawal and other traditional methods.

[d] More developed: Europe, USA/Canada, Australia/New Zealand, Japan

[e] Less developed: Latin America and the Caribbean, Africa, Asia (except Japan), Oceania (except Australia and New Zealand)

Yuzpe (2002) reported that 17% of women of reproductive age in the USA were current users of oral contraceptives in 1995. In 2000, it was estimated that there were more than 10 million users in the USA, and that use was more common among younger women. In the USA, 80% of women born after 1945 have used oral contraceptives at some time (Blackburn *et al.*, 2000).

1.4.2 *Trends in prevalence*

Information on trends over time also indicates substantial heterogeneity between countries. Different investigators have reached contradictory conclusions on whether worldwide use is increasing or remains constant. Bongaarts and Johansson (2000) tracked changes in combined oral contraceptive use in the developing world and projected that it would double between 1993 (11% of women) and 2015 (22%). This trend is attributed to improved access, changes in the characteristics of users with better education, a desire for smaller families and new and improved technology. In contrast, Zlidar *et al.* (2003) suggested that use among married women had been more or less constant in 38 developing countries since 1990. However, Blackburn *et al.* (2000) noted very large increases in oral contraceptive use in Bangladesh (from 3 to 21%), Kenya (from 3 to 9%) and Morocco (from 13 to 32%) between 1978 and 1998, while rates declined or remained similar in Colombia, India and Egypt during the same period. A United Nations analysis of data on trend suggested little net change over time. Substantial variations were noted, however, with sizeable increases or decreases in selected countries (United Nations, 2004a).

Data on sales of combined hormonal contraceptives (IMS Health, 2005) confirmed many of the data on prevalence observed in the United Nations data compilation, but indicated increasing use worldwide (Table 2). A worldwide increase of 19% between 1994 and 1999 and a subsequent 21% increase from 1999 to 2004 were noted. The largest relative increases occurred in eastern Europe, the eastern Mediterranean, South-East Asia and the western Pacific. Only modest increases were observed in Africa and South America. It should be noted that these data may not include large quantities of hormonal contraceptives that are provided by national and international family planning programmes. Several other trends are indicated from the sales data: (i) the use of higher estrogen doses (≥ 50 μg) has continued to decline; (ii) growth in the use of products that contain later progestogens (gestodene, desogestrel) has slowed down and in some countries there has been a shift back to earlier progestogens (norethynodrel, norethisterone); and (iii) monophasic hormonal formulations have continued to predominate with some shift away from multiphasic forms (IMS Health, 2005).

On the basis of case–control data from several large cities in the USA, the most frequent duration of use among controls was 1–5 years, although some women reported use for more than 15 years (Marchbanks *et al.*, 2002).

While most use of combined hormonal contraception is for on-going contraception, additional common indications include emergency contraception, regulation of menstrual disorders and treatment of acne. In a study of use in Dutch adolescents (14–17 years old),

Table 2. Trends in sales of combined hormonal contraceptives for selected years (millions of standard units[a])

Regions[b]	1994	1999	2004
Africa	9.5	10.4	10.2
South Africa	8.9	9.7	9.5
West Africa	0.6	0.6	0.7
Eastern Mediterranean	14.8	16.7	20.7
Europe	259.3	293.4	338.1
Eastern Europe	14.3	31.9	46.0
Western Europe	245.0	261.5	292.2
North America	103.3	122.4	161.0
South America	91.1	103.6	110.9
South-East Asia	17.0	45.0	70.1
Bangladesh	6.4	4.2	6.9
India	0	22.1	15.4
Republic of Korea	2.7	2.3	2.9
Rest of South-East Asia	7.9	16.4	44.9
Western Pacific	21.7	24.7	34.6
Australia/New Zealand	16.5	16.6	15.9
China/Hong Kong	0.2	0.7	0.9
Japan	0	0.6	3.0
Taiwan, China	1.4	1.3	1.4
Rest of Western Pacific	3.6	5.4	13.5
Total	516.9	616.4	745.8

From IMS Health (2005)

[a] Standard units, sales in terms of standard dose units; the standard dose unit for oral products is one tablet or capsule.

[b] The countries were grouped according to the WHO classification:
West Africa includes: Benin, Burkina, Cameroon, Congo, Gabon, Guinea, Ivory Coast, Mali, Senegal, Togo;
Eastern Mediterranean includes: Egypt, Jordan, Kuwait, Lebanon, Morocco, Saudi Arabia, Tunisia, United Arab Emirates;
Eastern Europe includes: Belarus, Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Russian Federation, Slovakia, Slovenia, Ukraine;
Western Europe includes: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, United Kingdom;
North America includes: Canada, Central America (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama), Mexico, Puerto Rico, USA;
Rest of South-East Asia includes: Indonesia, Pakistan, Thailand;
South America includes: Argentina, Brazil, Chile, Colombia, Dominican Republic, Ecuador, Peru, Uruguay, Venezuela;
Rest of Western Pacific includes: Malaysia, Philippines, Singapore.

current use for indications other than contraception (34%) included use for irregular cycles (18%), dysmenorrhoea (25%) and acne (11%) (van Hooff *et al.*, 1998).

The characteristics of women who use combined contraceptives differ from those who do not. Use appears to be more frequent among women who are younger and more highly educated, and increases with access to modern contraceptives (Piccinino & Mosher, 1998; Ross *et al.*, 2002).

Characteristics of users depend on regional differences and have evolved over time. Women have gradually begun to use oral contraceptives at younger ages, and initiation of use at 15–19 years of age is now frequent, while in the past it tended to start at 20–24 years of age. One study in the Netherlands reported a large increase in use among 15–17-year-old girls (Van Hooff *et al.*, 1998). In contrast, Piccinino and Mosher (1998) observed a decline in use among teenagers between 1988 and 1995 in the USA.