ORAL CONTRACEPTIVES, COMBINED

1. Exposure

Combined oral contraceptives consist of the steroid hormone oestrogen in combination with a progestogen, taken primarily to prevent pregnancy. The same hormones can also be used in other forms for contraception. Combined oral contraceptive pills generally refer to pills in which an oestrogen and a progestogen are given concurrently in a monthly cycle. In contrast, a cycle of sequential oral contraceptive pills includes oestrogen-only pills followed by five to seven days of oestrogen plus progestogen pills. Sequential oral contraceptive pills were removed from the consumer market in the late 1970s; they are covered in an IARC monograph (IARC, 1979, 1987). Combined oral contraceptives are thus usually administered as a pill containing oestrogen and progestogen, which is taken daily for 20–22 days, followed by a seven-day pill-free interval (or seven days of placebo), during which time a withdrawal bleed is expected to occur. The most commonly used oestrogen is ethinyloestradiol, although mestranol is used in some formulations. The progestogens most commonly used in combined oral contraceptives are derived from 19-nortestosterone and include norethisterone, norgestrel and levonorgestrel, although many others are available (Kleinman, 1990) (see Annex 2, Table 1).

Chemical and physical data and information on the synthesis, production, use and regulations and guidelines for hormones used in combined oral contraceptives are given in Annex 1. Annex 2 (Table 1) lists the trade names of many contemporary combined oral contraceptives with their formulations.

Combined oral contraceptives are currently available in monophasic, biphasic and triphasic preparations, the terms referring to the number of different doses of progestogen they contain. Monophasic pills maintain a constant dose of oestrogen and progestogen, while multiphasic pills allow a lower total dose of progestogen to be given by reducing the amount of progestogen early in the 20–22-day period of exposure. Biphasic pills contain a lower dose of progestogen early in the cycle followed by a higher dose in the last 11 days. Triphasic pills consist of three doses of progestogen, increasing through the cycle, which may or may not be accompanied by variations in the dose of oestrogen (Kleinman, 1990).

Sequential pills contain only oestrogen during the first part of the cycle and an oestrogen and progestogen thereafter. In older regimens, oestrogen was given alone for the first 16 days of the cycle, followed by five days of combined oestrogen and progestogen. These preparations were withdrawn from use in many countries in the 1970s after concern about their association with endometrial cancer (IARC, 1974, 1979). The sequential combined oral contraceptive regimens available currently include oestrogen alone for a

shorter interval, usually one week, followed by combined oestrogen and progestogen (Wharton & Blackburn, 1988; Kleinman, 1990).

Combined oral contraceptives act primarily by preventing ovulation, by inhibiting pituitary follicle-stimulating hormone and luteinizing hormone and by abolishing the pre-ovulatory surge in luteinizing hormone. The progestogen component renders the cervical mucus relatively impenetrable to sperm and may also reduce the receptivity of the endometrium to implantation (Williams & Stancel, 1996). Together, these actions make combined oral contraceptives very effective in preventing pregnancy, with fewer than one pregnancy per 100 users in the first year of use, when used correctly.

1.1 Historical overview

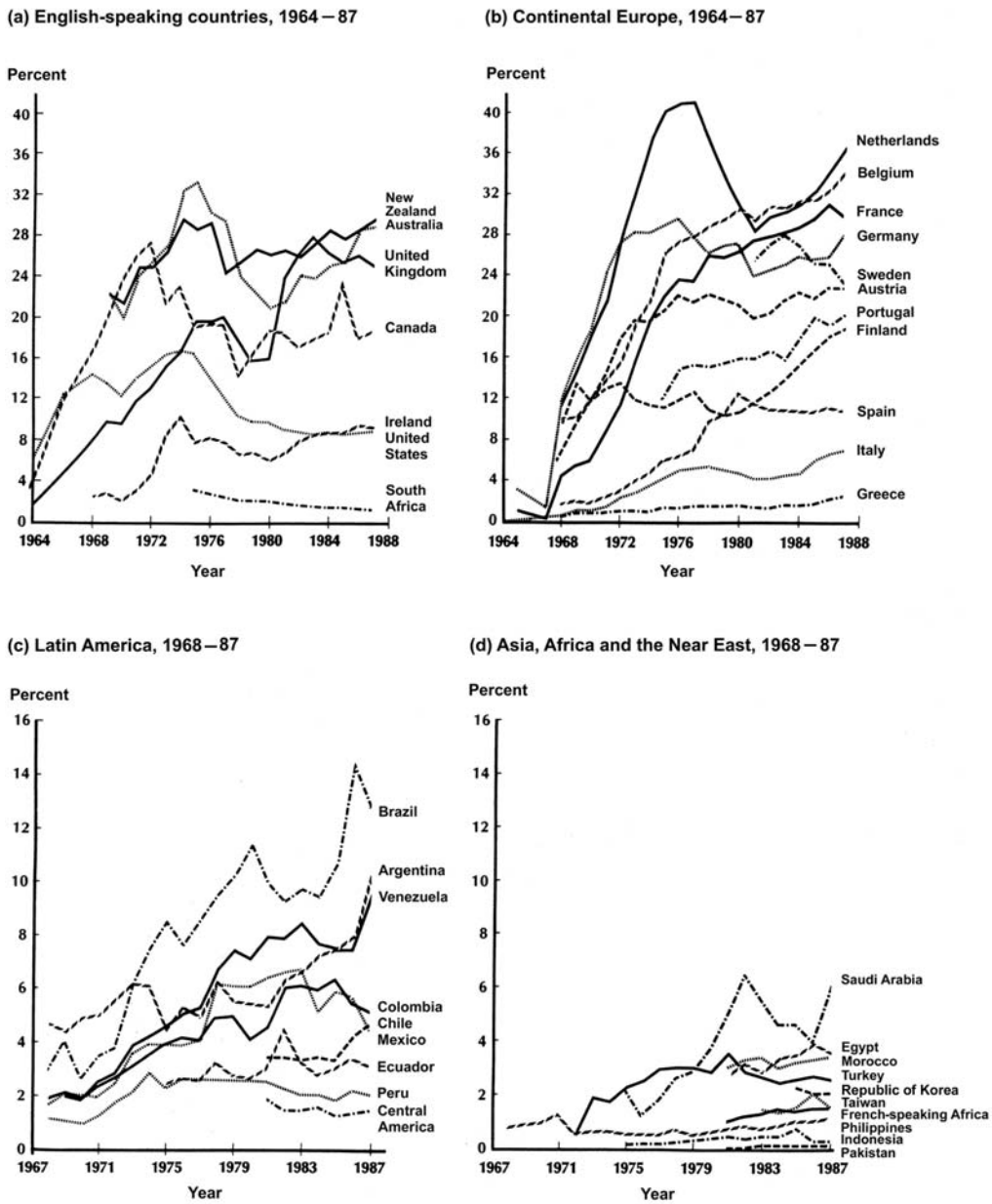
In the late nineteenth century, researchers noted that follicular development and ovulation were suppressed during pregnancy and that extracts of the corpus luteum inhibited ovulation in laboratory animals. In 1921, Ludwig Haberlandt proposed that extracts of the ovary itself could act as a contraceptive (Kleinman, 1990).

Three oestrogens were identified in 1929 and 1930, and progesterone was identified in 1934; however, there were no readily available oral equivalents until 1941, when Russell Marker synthesized diosgenin from extracts of the Mexican yam. Further experimentation yielded the synthesis of norethisterone (norethindrone in the United States) by Carl Djerassi in 1950 and norethynodrel by Frank B. Colton in 1952. These compounds were named progestogens (or progestins) due to their progesterone-like actions (Kleinman, 1990).

In the early 1950s, John Rock investigated the combination of oestrogen and progestogen for the treatment of infertility and found that women who were taking this compound did not ovulate. During 1956, Gregory Pincus, Celso-Ramon Garcia, John Rock and Edris Rice-Wray initiated clinical trials in Puerto Rico of the use of oral norethynodrel as a contraceptive. It was noted that the preparations containing the oestrogen mestranol as a contaminant were more effective in suppressing ovulation than those containing pure norethynodrel. In 1957, the combination of mestranol and norethynodrel was made available in the United States for regulation of menstruation, and in May 1960 it was approved as an oral contraceptive (McLaughlin, 1982; Kleinman, 1990). It was marketed as Enovid® and contained 150 μg mestranol and 9.35 mg norethynodrel (Thorogood & Villard-Mackintosh, 1993). Oral norethisterone (Norlutin®) was approved for menstrual regulation, but was not approved as an oral contraceptive until 1962, when it was combined with mestranol, as Ortho-Novum® (Drill, 1966). Interestingly, in 1959, about 500 000 women in the United States were taking Enovid® or Norlutin® for the treatment of ‘menstrual disorders’ (McLaughlin, 1982). Enovid® became available in the United Kingdom in 1960 (Thorogood & Villard-Mackintosh, 1993). Combined oral contraceptives were introduced throughout Europe and Latin America in the mid- to late 1960s, while use in many countries of Asia, Africa and the Middle East began in the 1970s and early 1980s (Wharton & Blackburn, 1988).

Figure 1 shows sales data for 1964–87 which have been converted into estimates of the percentages of women aged 15–44 buying the combined oral contraceptive pill from

Figure 1. Estimated percentages of women aged 15–44 buying oral contraceptives from pharmacies



Adapted from Wharton and Blackburn (1988)

pharmacies. It shows the rapid increase in the use of the combined oral contraceptive pill in North America, Australia, New Zealand and many European countries in the late 1960s and early 1970s, as well as the decline in use in some countries in the late 1970s, corresponding to the period when the adverse cardiovascular effects of the combined oral contraceptive pill were becoming apparent. They also show the lower but generally increasing rates of combined oral contraceptive use over that time in Latin America, Asia and Africa, although it is important to bear in mind that these figures do not include combined oral contraceptives donated by aid agencies, which constitute up to a third of use in these places (Wharton & Blackburn, 1988).

From the first combined oral contraceptive pill to those available at the time of writing, the doses of oestrogen and progestogen have decreased by at least threefold, and the compositions of treatments have changed, as has the timing of administration of the various component hormones (Piper & Kennedy, 1987). As noted above, the first combined oral contraceptive contained 150 μg mestranol (oestrogen) and 9.35 mg norethynodrel (progestogen); in 1963, just under 50% of combined oral contraceptive pills used by a sample of British women contained 100 μg oestrogen and the remainder contained at least 50 μg oestrogen (Thorogood & Villard-Mackintosh, 1993). Nausea, headaches, vomiting and other side-effects were already thought to be related to high oestrogen levels when research in Britain in the late 1960s linked high oestrogen doses to thromboembolic disease. This finding resulted in the development and prescription of lower-dose pills in the 1970s and 1980s, with the eventual phasing out of those containing more than 50 μg of oestrogen. These lower-dose combined oral contraceptives were found to be just as effective in preventing pregnancy as the high-dose pills, but with fewer side-effects (Wharton & Blackburn, 1988). Most of the combined oral contraceptives prescribed now contain less than 50 μg oestrogen (Wharton & Blackburn, 1988), a dose of 30–35 μg being standard and doses of 20 μg being available (Kleinman, 1990).

The dose of progestogen has also decreased over time, and many different types have been developed (see Annex 2, Table 1). Use of combined oral contraceptives containing a high dose of progestogen peaked in 1972 in the United States, with gradual decreases since, facilitated by the introduction of biphasic and triphasic pills in the 1980s, which allowed the use of even lower doses of progestogen (Piper & Kennedy, 1987; Wharton & Blackburn, 1988). The so-called 'new-generation' progestogens (desogestrel, gestodene and norgestimate) were introduced in the mid-1980s, promising lower doses with equivalent efficacy. Studies published around 1995 showed these compounds to be associated with higher rates of venous thromboembolism than those seen with other progestogens (Jick *et al.*, 1995; Farley *et al.*, 1996), resulting in a decrease in the number of prescriptions of combined oral contraceptives containing new-generation progestogens.

1.2 Patterns of use of combined oral contraceptives

Over 200 million women worldwide have used combined oral contraceptives since 1960 (Kleinman, 1990), and over 60 million are using them currently (Wharton & Blackburn, 1988). The prevalence of combined oral contraceptive use varies enormously

by country and region. Table 1 shows the percentage of married women or women in union aged 15–49 using any form of contraception (including traditional methods) and the percentage taking oral contraceptives. Although progestogen-only oral contraceptives are generally included in this figure, they constitute a relatively small proportion of use, even in the countries where they are most commonly used (see the monograph on 'Hormonal contraceptives, progestogens only'). The percentages are derived mainly from the Demographic and Health Surveys conducted by the United States Aid to International Development.

In 1988, the highest rates of combined oral contraceptive use were found in Europe, with over 40% of women in union of reproductive age using combined oral contraceptives in Belgium, Germany, Hungary and the Netherlands; in most other western European countries and in Australia and New Zealand, current use was 20–40%. Lower rates of use were found in Mediterranean Europe, including Spain, Italy and Greece. Use in the Americas and South-East Asia was generally intermediate, representing around 10–20% of eligible women, while countries in North Africa and the Middle East showed considerable variation in rates of use. The low rates of use of combined oral contraceptives in many countries of sub-Saharan Africa probably reflect low rates of contraceptive use overall and are in keeping with the large 'ideal family size' reported in those countries (Wharton & Blackburn, 1988). The low use in many eastern European and former Soviet Union countries probably reflects reliance on other methods of birth control, including abortion, and use of intrauterine devices (Popov *et al*., 1993). Use of combined oral contraceptives is also uncommon in the Indian sub-continent. They are not licenced for contraceptive use in Japan, although high-dose preparations are available for the treatment of menstrual problems (Kleinman, 1996).

Patterns of use also vary from country to country. Table 2 shows the percentages of women who have ever used combined oral contraceptives by year of birth. The figures are those for the controls of population-based studies of use of combined oral contraceptives and breast cancer. Clearly, in the birth cohorts examined, any use of the pill depends on the age of the woman at the time combined oral contraceptives were introduced into a country as well as the overall prevalence and pattern of use. It is also clear that, in many countries in Europe and in Australia, New Zealand and North America, the vast majority of women born more recently will have taken combined oral contraceptives at some stage. In 1981, 81% of Swedish women aged 25–30 had ever used combined oral contraceptive pills, whereas in 1990–91, 88% of women born in 1960–65 had ever used them; 77% had begun use before the age of 20 (Ranstam & Olsson, 1993). In a United States survey conducted between 1976 and 1980, 15% of 15–19-year-olds and 34% of 20–24-year-olds were currently using combined oral contraceptives (Russell-Briefel *et al*., 1985). In this context, it is important to note that women in high-prevalence countries who have never taken combined oral contraceptives may have particular characteristics, such as psychiatric illness. Indeed, in Sweden, women who have taken combined oral contraceptives are more likely to smoke, drink alcohol, be cohabiting, be older at their first full-term pregnancy and younger at menarche than women who have never taken them (Ranstam & Olsson, 1993).

Table 1. Contraceptive use among married women or women in union, aged 15–49, by country

Country or region	Year of survey	Any method (%)	Oral contra-ceptives (%)	No. of women (in thousands, 1990)	Calculated no. of oral contra-ceptive users (thousands)
Africa					
Algeria	1986–87	36	27		
	1992	51	39	3 300	1 287
Benin	1982	27	0		
	1996	16	1	800	8
Botswana	1984	28	10		
	1988	33	15	100	15
Burkina Faso	1993	8	2	1 600	32
Burundi	1987	9	0.25	800	2
Cameroon	1978	3	0		
	1991	16	1	1 600	19
Central African Republic	1994	15	1	500	5
Comoros	1996	21	3	75	2.2
Côte d'Ivoire	1980–81	4	1		
	1994	11	2	1 900	42
Egypt	1980	24	16		
	1984	30	17		
	1988	38	15		
	1991	48	16		
	1992	47	13		
	1995	48	10	8 300	863
Eritrea	1995	8	2		
Ethiopia	1990	4	2	8 300	158
Gambia	1990	12	3	100	3
Ghana	1979–80	12	3		
	1988	13	2		
	1993	20	3		
	1995	28	7	2 300	161
Kenya	1977–78	7	2		
	1984	17	3		
	1989	27	5		
	1993	33	10	3 100	298
Lesotho	1977	7	2		
	1991–92	23	7	200	14
Liberia	1986	6	3	400	13
Madagascar	1992	17	2	1 700	26
Malawi	1984	7	1		
	1992	13	2	1 400	31
Mali	1987	5	1		
	1995–96	7	3	1 900	59

Table 1 (contd)

Country or region	Year of survey	Any method (%)	Oral contra-ceptives (%)	No. of women (in thousands, 1990)	Calculated no. of oral contra-ceptive users (thousands)
Africa (contd)					
Mauritania	1981	1	0		
	1990	4	1	300	3
Mauritius	1975	46	21		
	1985	75	21		
	1991	75	21	200	42
Morocco	1970	1	1		
	1971	3	2		
	1972	4	3		
	1973	6	5		
	1974	7	6		
	1979	16	13		
	1979–80	19	13		
	1983–84	26	16		
	1987	36	23		
	1992	42	28		
	1995	50	32	3 300	1 063
Namibia	1989	26	7		
	1992	29	8	100	8.3
Niger	1992	4	2	1 300	20
Nigeria	1981–82	6	0		
	1990	6	1	18 100	217
Réunion	1990	73	40	100	40
Rwanda	1983	10	0		
	1992	21	3	900	27
Senegal	1978	4	0		
	1986	11	1		
	1992	7	2	1 200	26
South Africa	1975–76	50	14		
	1981–82	48	14		
	1988	50	13	4 300	568
Sudan	1979	5	3		
	1989–90	9	4		
	1992–93	10	5	3 700	185
Swaziland	1988	20	5	100	5.5
Togo	1988	34	0	600	2.4
Tunisia	1978	31	7		
	1983	41	5		
	1988	50	9		
	1994–95	60	7	1 100	80

Table 1 (contd)

Country or region	Year of survey	Any method (%)	Oral contra-ceptives (%)	No. of women (in thousands, 1990)	Calculated no. of oral contra-ceptive users (thousands)
Africa (contd)					
Uganda	1988–89	5	1		
	1995	15	3	2 600	68
Zambia	1992	15	4	1 200	52
Zimbabwe	1979	14	5		
	1984	38	23		
	1988	43	31		
	1994	48	33	1 400	463
Europe					
Austria	1981–82	71	40	1 200	480
Belgium	1966	72	5		
	1975	87	30		
	1982	81	32		
	1991	80	47	1 700	792
Bulgaria	1976	76	2	1 600	32
Czech Republic	1993	69	8	1 700	138
Denmark	1970	67	25		
	1975	63	22		
	1988	78	26	700	182
Finland	1971	77	20		
	1977	80	11		
	1989	70	15		
	1994	79	31	700	214
France	1972	64	11		
	1978	79	27		
	1988	80	27		
	1994	75	37	8 500	3 137
Germany	1985	78	34		
	1992	75	59	12 000	7 080
Hungary	1966	67	0		
	1974	74	27		
	1977	73	36		
	1986	73	39		
	1993	84	41	1 800	742
Italy	1979	78	14	9 600	1 344
Lithuania	1994–95	66	5	600	28

Table 1 (contd)

Country or region	Year of survey	Any method (%)	Oral contra-ceptives (%)	No. of women (in thousands, 1990)	Calculated no. of oral contra-ceptive users (thousands)
Europe (contd)					
Netherlands	1969	59	27		
	1975	75	50		
	1977	73	40		
	1982	69	39		
	1985	72	40		
	1988	70	43		
	1993	74	47	2 200	1 034
Norway	1977	71	13		
	1988	76	18	500	89
Poland	1972	60	2		
	1977	75	7	6 400	448
Portugal	1979–80	66	19	1 800	344
Romania	1978	58	1		
	1993	57	3	3 800	122
Slovakia	1991	74	5	1 000	50
Slovenia	1989	92	25		
Spain	1977	50	12		
	1985	59	16	6 400	992
Sweden	1981	78	23	1 200	276
Switzerland	1980	71	28		
	1994	82	34	1 000	341
United Kingdom	1970	75	19		
	1975	76	30		
	1976	77	32		
	1983	83	24		
	1986	81	19		
	1989	72	25	9 300	2 325
North America					
Canada	1984	73.1	11	4 200	462
United States	1965	63	15		
	1973	70	25		
	1976	68	23		
	1982	70	13		
	1988	74	15		
	1990	71	15	35 800	5 191
Latin America and the Caribbean					
Bolivia	1983	24	3		
	1989	30	2		
	1994	45	3	1 000	28

Table 1 (contd)

Country or region	Year of survey	Any method (%)	Oral contra-ceptives (%)	No. of women (in thousands, 1990)	Calculated no. of oral contra-ceptive users (thousands)
Latin America and the Caribbean (contd)					
Brazil	1986	66	25		
	1996	77	21	23 700	4 906
Colombia	1969	28	5		
	1976	43	14		
	1978	46	17		
	1980	49	17		
	1984	55	21		
	1986	65	16		
	1990	66	14		
	1995	72	13	4 700	606
Costa Rica	1976	68	23		
	1978	64	25		
	1981	65	21		
	1984	65	23		
	1986	68	19		
	1992–93	75	18	400	72
Cuba	1987	70	10	1 900	190
Dominican Republic	1975	32	8		
	1977	31	8		
	1980	42	9		
	1983	28	5		
	1986	50	9		
	1991	56	10		
	1996	64	13	1 000	129
Ecuador	1979	35	10		
	1982	40	10		
	1987	44	9		
	1989	53	9		
	1994	57	10	1 700	173
El Salvador	1975	22	7		
	1976	20	6		
	1978	34	9		
	1985	47	7		
	1988	47	8		
	1993	53	9	700	61
Guadeloupe	1976	44	10	100	10
Guatemala	1978	19	6		
	1983	25	5		
	1987	23	4		
	1995	31	4	1 300	49

Table 1 (contd)

Country or region	Year of survey	Any method (%)	Oral contra-ceptives (%)	No. of women (in thousands, 1990)	Calculated no. of oral contra-ceptive users (thousands)
Latin America and the Caribbean (contd)					
Guyana	1975	32	10	200	20
Haiti	1977	19	3		
	1983	7	2		
	1987	8	3		
	1989	10	4		
	1994	18	3	1000	31
Honduras	1981	27	12		
	1984	35	13		
	1987	41	13	700	94
Jamaica	1975–76	41	13		
	1979	55	24		
	1983	51	27		
	1989	55	20		
	1993	62	22	400	86
Martinique	1976	51	17	100	17
Mexico	1973	13	11		
	1976	29	12		
	1978	26	9		
	1979	38	15		
	1982	50	14		
	1987	53	10	13 000	1 261
Nicaragua	1981	27	11		
	1992–93	49	13	500	65
Panama	1976	57	19		
	1979	61	19		
	1984	58	12	300	35
Paraguay	1977	29	12		
	1979	32	10		
	1987	45	13		
	1990	48	14		
	1995–96	56	14	600	81
Peru	1969–70	26	3		
	1977–78	41	5		
	1981	41	5		
	1986	46	7		
	1991–92	59	6		
	1996	64	6	300	19

Table 1 (contd)

Country or region	Year of survey	Any method (%)	Oral contra-ceptives (%)	No. of women (in thousands, 1990)	Calculated no. of oral contra-ceptive users (thousands)
Latin America and the Caribbean (contd)					
Puerto Rico	1968	60	11		
	1974	62	20		
	1976	65	13		
	1982	70	9		
	1995–96	78	10	500	49
Trinidad and Tobago	1970–71	44	17		
	1977	54	19		
	1987	53	14	200	28
Venezuela	1977	60	19	2 700	506
Asia					
Bahrain	1989	53	13	100	13
Bangladesh	1975	8	3		
	1977	9	2		
	1979	13	4		
	1980	12	4		
	1981	20	4		
	1983	19	3		
	1985	25	5		
	1989	31	9		
	1991	40	14		
	1993	45	17	21 400	3 724
Burma	1991	17	4		
China	1982	70	6		
	1988	71	4		
	1992	77	3	222 700	5 968
Hong Kong	1969	42	16		
	1972	54	20		
	1977	77	28		
	1982	77	21		
	1984	72	22		
	1987	81	16	900	148
India	1980	32	1		
	1988	43	1		
	1992–93	41	1	159 000	1 908
Indonesia	1973	9	3		
	1976	26	15		
	1979	21	11		
	1980	26	14		
	1985	39	15		

Table 1 (contd)

Country or region	Year of survey	Any method (%)	Oral contra-ceptives (%)	No. of women (in thousands, 1990)	Calculated no. of oral contra-ceptive users (thousands)
Asia (contd)					
Indonesia (contd)	1987	51	18		
	1991	50	15		
	1994	55	17	31 400	5 369
Iran	1978	23	20		
	1992	65	23	9 200	2 116
Iraq	1974	14	8		
	1989	14	5	2 500	117.5
Japan	1969	52	1		
	1971	53	1		
	1973	59	1		
	1975	61	2		
	1977	60	2		
	1979	62	2		
	1984	57	1		
	1986	64	1		
	1988	56	1	18 600	186
Jordan	1972	21	13		
	1976	25	12		
	1983	26	8		
	1985	27	6		
	1990	35	5	500	23
Kuwait	1987	35	24	300	72
Malaysia	1966–67	9	4		
	1970	16	12		
	1974	36	18		
	1979	36	25		
	1981	42	17		
	1984	51	12		
	1988	48	15	2 600	390
Nepal	1976	3	1		
	1981	7	1		
	1986	15	1		
	1991	25	1		
	1996	29	1	3 500	49
Oman	1988	9	2	200	4.8
Pakistan	1975	4	1		
	1980	6	1		
	1984–85	9	1		
	1990–91	12	1	18 100	127

Table 1 (contd)

Country or region	Year of survey	Any method (%)	Oral contra-ceptives (%)	No. of women (in thousands, 1990)	Calculated no. of oral contra-ceptive users (thousands)
Asia (contd)					
Philippines	1968	15	1		
	1972	8	5		
	1973	18	7		
	1976	22	11		
	1977	22	11		
	1978	37	5		
	1979	37	6		
	1980	45	5		
	1981	48	16		
	1983	33	6		
	1988	36	7		
	1993	40	9		
	1995	53	11		
	1996	48	12	9 700	1 125
Quatar	1987	32	13	100	13
Republic of Korea	1991	79	3	7 600	228
Singapore	1970	45	38		
	1973	60	22		
	1977	71	17		
	1978	71	17		
	1982	74	12	500	57.9
Sri Lanka	1975	32	2		
	1982	55	3		
	1987	62	4	2 700	110.7
Thailand	1970	14	4		
	1973	26	11		
	1975	33	14		
	1978	53	22		
	1981	59	20		
	1984	65	20		
	1985	59	21		
	1987	66	19	9 000	1 674
Turkey	1963	22	1		
	1968	32	2		
	1973	38	4		
	1978	50	8		
	1983	51	8		
	1988	63	6		
	1993	63	5	9 400	461

Table 1 (contd)

Country or region	Year of survey	Any method (%)	Oral contra-ceptives (%)	No. of women (in thousands, 1990)	Calculated no. of oral contra-ceptive users (thousands)
Asia (contd)					
Viet Nam	1988	53	0		
	1994	65	2	10 000	210
Yemen	1979	1	1		
	1991–92	7	3	1 700	54
Oceania					
Australia	1986	76	24	2 600	624
New Zealand	1976	70	29	400	114

From Population Council (1994, 1995); Phai *et al*. (1996); Population Council (1996a,b); United Nations (1996); Population Council (1997a,b,c,d,e,f; 1998a,b); United States Census Bureau (1998)

Sales figures for 1987 show that more than 40% of oral contraceptives purchased by pharmacies in most 'developed' countries were monophasic preparations, containing less than 50 μg oestrogen; approximately 35% were triphasic preparations, 10% were monophasic preparations containing 50 μg oestrogen, about 8% were biphasic preparations containing less than 50 μg oestrogen, about 3% were sequential combined preparations, and around 2% contained progestogen alone. In 'developing' countries, just under 50% of preparations bought by pharmacies were monophasic preparations containing less than 50 μg oestrogen, approximately 10% were triphasic preparations and around 42% were monophasic preparations containing 50 μg oestrogen (Wharton & Blackburn, 1988). Most of the oral contraceptives provided by major aid organizations (United States Aid to International Development, United Nations Family Planning Agency, International Planned Parenthood Federation) contain 30 μg ethinyloestradiol and 150 μg levonorgestrel.

1.3 Exposure to other combinations of oestrogen and progestogen

Injectable combined hormonal contraceptives were first developed in the late 1960s and consist of a depot progestogen and oestrogen administered monthly. Formulations and brands of such preparations are listed in Table 3, with a list of some of the countries in which they are available. They are used in parts of Latin America, China, Spain, Portugal, Thailand, Indonesia and Singapore, although, as can be seen from Table 1 in the monograph on 'Hormonal contraceptives, progestogens only', they are unlikely to constitute a large proportion of the contraceptive use in these countries.

In Latin America, at least 1 million women use dihydroxyprogesterone acetophenide and oestradiol oenanthate, and the combination of dihydroxyprogesterone acetophenide

Table 2. Percentages of women who have ever used oral contraceptives, by year of birth

Country	Year of birth							
	< 1915	1915–19	1920–24	1925–29	1930–34	1935–39	1940–44	1945–49
Australia	0	3	18	36	55	69	80	85
Canada	1	6	26	42	53	67	79	84
China	–	–	1	2	19	36	39	39
Denmark	–	0	4	21	35	46	66	75
France	–	–	–	7	16	38	61	69
Germany	–	–	–	–	40	58	75	86
Italy	0	0.4	0.2	2	3	8	15	25
Netherlands	–	5	16	35	49	69	84	90
New Zealand	–	–	–	50	61	75	84	91
Norway	–	–	–	–	–	–	–	45
Sweden	–	–	–	–	–	–	65	82
United Kingdom	–	3	15	27	41	51	68	83
United States	1	4	14	28	43	60	75	85

From Collaborative Group on Hormonal Factors in Breast Cancer (1996a) Appendix 5

Table 3. Injectable contraceptives containing oestrogen and progesterone given monthly

Brand name	Composition	Dose (mg)	Availability
Anafertin, Yectames	Oestradiol oenanthate Dihydroxyprogesterone acetophenide	5 75	Many Latin American countries and Spain
Chinese injectable No. 1	Oestradiol valerate 17α-Hydroxyprogesterone caproate	5 250	China
Chinese injectable No. 2	Oestradiol Megestrol acetate	3.5 25	China
Cicnor, Damix, Progesterol, Segutalmes	Oestradiol oenanthate Medroxyprogesterone acetate	10 150	Portugal
Ciclofem, Ciclofemina, Cyclofem, Cyclo Geston	Oestradiol cypionate Medroxyprogesterone acetate	5 25	Registered in Guatamala, Indonesia, Mexico, Peru and Thailand
Chinese injectable No. 3, Mesigyna, Norigynon	Oestradiol valerate Norethisterone oenanthate	5 50	Argentina, Brazil and Mexico
Agurin, Ciclovar, Deproxone, Exuna, Horprotal, Neolutin, Normagest, Novular, Perlutal, Perlutale, Perlutan, Proter, Topasel, Uno Ciclo	Oestradiol oenanthate Dihydroxyprogesterone acetophenide	10 150	Many Latin American countries and Spain
Redimen, Soluna, Unijab	Oestradiol benzoate Dihydroxyprogesterone acetophenide	10 150	Peru and Singapore
Unalmes	Oestradiol oenanthate Alfasona acetophenide	10 120	Chile and Paraguay

From Kleinman (1990); Lande (1995)

and hydroxyprogesterone caproate (Chinese injectable No. 1) has been used by about 1 million women in China (Lande, 1995).

A relatively high dose of oestrogen and progestogen can be administered up to 72 h after unprotected intercourse as 'emergency contraception'. It is often given as 100 μg ethinyl-oestradiol and 0.5 mg levonorgestrel (or 1 mg norgestrel), as two tablets, immediately and a further equal dose 12 h later (Kleinman, 1990). A progestogen-only regimen is also available (see the monograph on 'Hormonal contraceptives, progestogens only').