Part 7: Clinical Application and Potential of Estrogens and Antiestrogens

CHAPTER 38

Hormonal Contraception

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H. KUHL

A. History

Ovulation inhibition by progestogens was postulated as early as 1921 by HABERLANDT. One year later, a similar action was ascribed to estrogens by FELLNER. In 1944, BICKENBACH and PAULIKOVICS succeeded in suppressing ovulation in a woman by means of daily injections of 20 mg progesterone. Hormonal contraception for all women, however, only became possible after orally active estrogens and progestogens had been developed. The basis for this revolution in birth control was brought about by BUTENANDT, INHOFFEN, HOHLWEG, MARKER, DJERASSI and many other scientists.

The first report of an ovulation-inhibiting effect of the synthetic progestogens, norethisterone and norethynodrel, was published in 1956 by ROCK, PINCUS and GARCIA. In 1958, the results of a large field study demonstrated that a combination of high doses of mestranol (ME) and norethynodrel effectively prevents pregnancy. The first oral contraceptive "Enovid" was approved in the USA in 1960 and contained 150 μg ME and 9.85 mg norethynodrel. "Anovlar" which was introduced in Germany 1 year later, was, at that time, regarded as a very low dose formulation (50 μg ethinylestradiol and 4 mg norethisterone acetate). Until today, ethinylestradiol has remained the estrogen of choice in oral contraceptives.

The results of some large prospective studies, initiated between 1968 and 1970 in England and USA, indicated that oral contraceptives, particularly their estrogen component, may be involved in the development of venous thromboembolic diseases and other complications and disorders. As a consequence, the dose of ethinylestradiol was considerably reduced and new progestogens were developed. The first sequential ovulation inhibitor was marketed in Germany in 1964, and the first triphasic formulation was introduced in 1979, also in Germany. The first estrogen-free preparation, the "mini-pill", which consists of a low-dose progestogen only, was introduced in 1965 in Mexico. In the same country, the first depot-progestogen became available 1 year later. Until this day, many hormonal systems and formulations have been developed that differ in their composition and route of administration, in their efficacy and risk profile. It can, however, be expected that ovulation inhibitors will remain the leading method among the hormonal contraceptives.

B. Types of Hormonal Contraceptives

I. Progestogen-Only Contraceptives

Women with contraindications for ethinylestradiol (EE) or women who do not tolerate estrogen containing formulations may use progestogen-only preparations or non-hormonal methods. The hormonal and non-hormonal methods differ largely in their practicability, efficacy and risks.

1. Mini-pill

Among the progestogen-only preparations, the mini-pill exerts the least impact on metabolism and the least contraceptive efficacy, although it is taken continuously without a hormone-free interval (Table 1). It consists of a progestogen at a very low dose, the effect of which lasts for merely 24 h. Therefore, the mini-pill has to be taken regularly at the same time of day. The contraceptive efficiency of the mini-pill is based on its progestogenic effect on cervical mucus, endometrium and tubal function, which impairs or prevents migration and capacitation of sperms, synchronous transport of the zygote and

Table 1. Failure rate during the first year of use, reversibility and health risk of various contraceptive methods. (Modified from MCCANN and POTTER 1994)

Method	PI-1	PI-2	Reversibility	Risk
No method	85	85		
Female sterilization	0.2	0.4	Limited	Very low
Male sterilization	0.1	0.15	Limited	Very low
Ovulation inhibitor	0.1	1	Yes	Low
Mini-pill	0.5	3	Yes	Very low
Depot-progestogen (MPA)	0.3	0.3	Yes	Very low
Depot-progestogen (NETE)		1.5	Yes	Very low
Norplant	0.3	0.3	Yes	Very low
Intrauterine device (Cu)	0.6	0.8	Yes	Low
Intrauterine device (LNG)	0.1	0.1	Yes	Very low
Diaphragm + spermicide	6	18	Yes	None
Cervical cap (parous women)	9	28	Yes	None
Cervical cap (nulliparous women)	6	18	Yes	None
Spermicide	6	21	Yes	None
Sponge (parous women)	20	36	Yes	None
Sponge (nulliparous women)	9	18	Yes	None
Female condom	5	21	Yes	None
Male condom	3	12	Yes	None
Coitus interruptus	4	19	Yes	None
Periodic abstinence		20	Yes	None
Calendar method	9	–	–	–
Basal temperature	3	–	–	–
Sympto-thermal	2	–	–	–

PI-1, Pearl-Index when correctly used; PI-2, Pearl-Index in reality; MPA, medroxyprogesterone acetate; NETE, norethisterone enanthate; Cu, copper; LNG, levonorgestrel

implantation (McCann and Potter 1994). In addition, in about one-third of the women, ovulation is inhibited. In young women, the Pearl Index is approximately 3 (Table 1), but is improved in older women (Vessey et al. 1985). The mini-pill is the method of choice for contraception during lactation, as it does not adversely influence infant growth and development (World Health Organization 1994a, b). It should not be used by patients with endometriosis, uterine myoma or mastopathia, as frequently high endogenous estradiol levels can be observed. The relative risk of ectopic pregnancy is increased; therefore, it is contraindicated in women with a history of tubal pregnancy.

2. Depot-Progestogens

The high effectiveness of depot-medroxyprogesterone acetate (depot-MPA), the norplant systems or the levonorgestrel containing intrauterine device (LNG-IUD) is based on the permanent and relatively even influence of a progestogen which is ensured by the hormone depot. The intramuscular injection of depot-MPA (150 mg) effectively suppresses ovulation for at least 18 weeks and, after a transitory period of irregular bleeding, causes amenorrhea during consecutive injections every 3 months. The ovulation-inhibiting action of norethisterone enanthate, however, lasts for only 6–8 weeks after the injection and, thereafter, the contraceptive effect depends on the peripheral progestogenic changes caused in the cervical mucus, tubes and endometrium (Population Reports 1995). In order to increase efficacy, the first injections of norethisterone enanthate (200 mg) are carried out every 2 months and, thereafter, every 3 months.

After the subdermal implantation of Silastic capsules or rods containing levonorgestrel (Norplant), a low but relatively even serum concentration of the progestogen is achieved which causes a reliable contraception for 3–5 years, based on the peripheral effects on cervix, tubes and endometrium (Population Reports 1992). In addition, in half of the cycles, ovulation is inhibited. After insertion of the LNG-IUD, the strong local effect of LNG on the endometrium and cervical mucus warrants a highly effective contraception, while the systemic effect of the progestogen is negligible.

II. Estrogen/Progestogen-Containing Contraceptives

1. Post-coital Pill

In the case of a suspected failure of contraception, an emergency measure may become necessary. Previously it was shown that the use of high doses of estrogens (e.g., 5 mg ethinylestradiol for 5 days) may prevent implantation. As this method was frequently associated with gastrointestinal side effects and bleeding, another regimen was investigated and proved to be effective. The intake of two tablets containing 50 μg EE and 250 μg LNG, not later than 72 h after intercourse, and another two tablets of this high dose ovulation inhibitor (total dose 200 μg EE + 1 mg LNG) 12 h later, prevents implantation in 98% of cases

(YUZPE et al. 1982). This "morning-after" or post-coital pill is not suitable as a normal contraceptive method, as the following cycle may be disturbed. The mechanism of action is not clear, but it is suggested that tubal function and endometrium are profoundly affected, resulting in the prevention of implantation (HASPELS 1994). The side effects, which are less severe than those after use of high-dose estrogens, are nausea, vomiting, breast tenderness, dizziness and headaches. It is also recommended to use an anti-emetic. The patient should be followed up for 3 weeks in order to assess the result. If the time limit of 72 h is passed, the insertion of a copper intrauterine device within 5 days after intercourse may also prevent implantation.

2. Ovulation Inhibitors

Ovulation inhibition can be achieved by means of a prolonged influence of sufficient concentrations of a potent estrogen and/or a potent progestogen. Therefore, the contraceptive efficacy is essentially dependent on correct use and good compliance. Ovulation inhibitors, generally called "oral contraceptives" (OC) represent a combination of an estrogen, EE or ME, with a progestogen which is taken orally, daily, for 21 days or 22 days of the 28-day cycle (Fig. 1). There are monophasic and bi- or triphasic (two- or tri-step formulations) combinations with varying doses of the estrogen and/or the progestogen component. The sequential type of OC consists of a first short phase, with estrogen only, and a second phase with a combination of EE and progestogen. Ovulation inhibitors are not only very reliable and easy-to-use contraceptives, but may influence many organs, tissues and metabolic systems, and may also cause adverse effects.

The modern OC consists of EE at a relatively low dose and a potent progestogen. Formulations containing 35 μg or less EE are called "micro-pills", irrespective of the progestogen component. The doses of the various progestogens used in OC depend on their hormonal potency. The impact on metabolism of different progestogens cannot be compared on the basis of the respective doses, as combinations with a low-dose potent progestogen may be more reliable, although may also cause more adverse effects than those with a less-potent compound at a higher dose.

The monophasic combinations represent the most effective OC, as the progestogen components exert their various contraceptive effects from the first day of the pill cycle. They consist of 21 tablets of the estrogen/progestogen combination at a fixed dose. The most effective preparations are those containing the progestogen at a dose which is about twice that of the respective ovulation inhibition dose (Table 2) (KUHL 1996a). The use of formulations with 23 tablets per cycle, i.e., the shortening of the hormone-free interval to only 5 days, will enhance contraceptive efficacy.

The bi- and triphasic OC consists of an estrogen and a progestogen which are combined at two or three different dosage combinations. Biphasic formulations may contain a constant estrogen dose, while the progestogen dose is

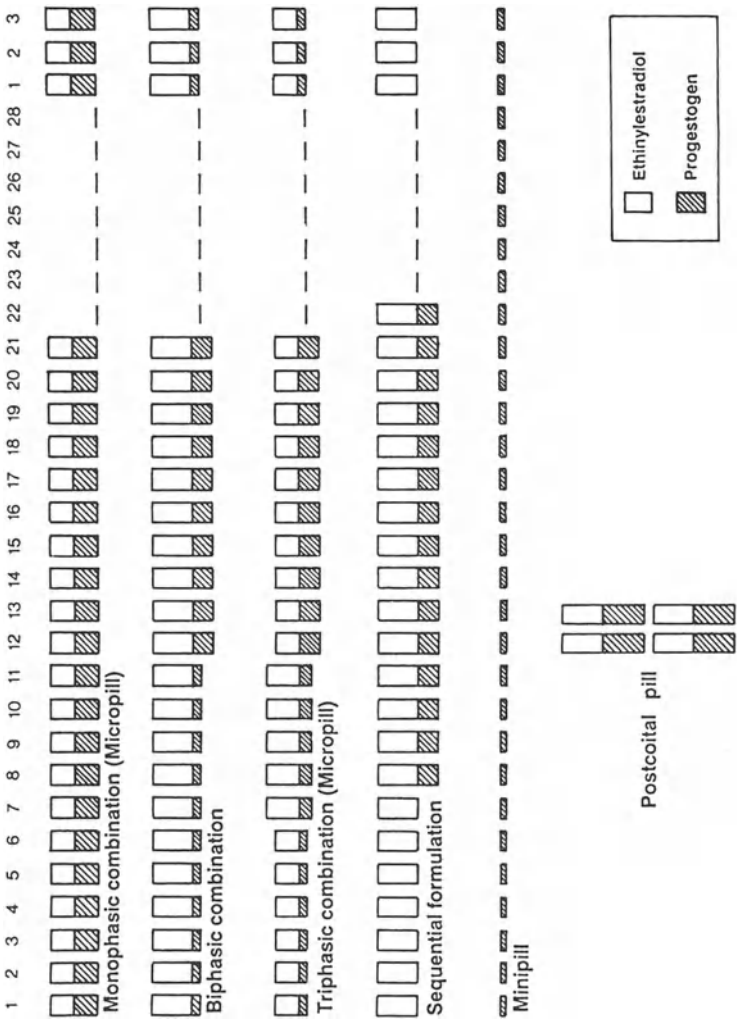

Fig. 1. Graphic representation of various types of hormonal contraceptives

Table 2. Hormonal potency of progestogens

Progestogen	T-Dose mg/cycle	OI-Dose mg/day	Dose (COMB)	Dose (PHAS)	AA (%)
Cyproterone acetate	12	1.0	2.0		100
Chlormadinone acetate	25	1.7	2.0	1.0	30
Dienogest	6	1.0	2.0		33
Norgestimate	7	0.2	0.25	0.18	
Levonorgestrel	4	0.06	0.125	0.05	
Norethisterone	100	0.4	0.5	0.5	
Norethisterone acetate	50	0.5	0.6		
Lynestrenol	70	2.0	0.75		
Desogestrel	2	0.06	0.150	0.125	
Gestoden	3	0.03	0.075	0.05	

T-Dose, transformation dose; OI-Dose, ovulation inhibition dose without estrogen; AA, relative anti-androgenic potency; COMB, combined OC; PHAS, first phase of bi- or triphasic OC

lower during the first phase. Triphasic OCs may consist of a constant estrogen dose and a step-wise increase in the progestogen dose, or a higher estrogen dose during the second phase and a step-wise increase in the progestogen doses (Fig. 1). Obviously, there is no advantage in the bleeding pattern or contraceptive efficacy of phasic pills compared with the monophasic formulations. From a theoretical point of view, the contraceptive efficiency of phasic pills must be less than those of monophasic formulations, as the progestogen dose is lower during the first week of intake.

This also holds true for the sequential formulations, the first phase of which consists of six or seven tablets with 50 μg EE only, while the second phase of 15 tablets represents an estrogen/progestogen combination. As the treatment with EE only at a dose of 50 μg during the first week does not inhibit follicular maturation reliably, ovulation may occur in some women. Moreover, there is no progestogenic influence on cervical mucus during the first week of use. On the other hand, the unopposed action of EE on the endometrium during the first phase allows the full proliferation of the endometrium, while the subsequently ingested estrogen/progestogen combination causes a secretory transformation that is similar to that during the luteal phase of an ovulatory cycle. Women taking sequential formulations show very good cycle control; therefore, this type of OC is the treatment of choice for women who suffer from irregular bleeding when taking combination or phasic pills. The first sequential OC which was introduced in the USA in 1963, was removed from the market in 1976 as a consequence of increased reports of endometrial carcinoma. This adverse effect was due to the short estrogen/progestogen phase of only 5–6 days. The modern sequential formulations which exert a progestogenic effect for 15 days per cycle protect from the development of endometrial hyperplasia and carcinoma.

C. Pharmacology of Contraceptive Steroids

I. Pharmacology of Estrogens

Since the introduction of the first OC, EE has remained the only active estrogen component. ME, which was contained in the first formulations and is still used in only a few OCs, represents the 3-methyl-ether of EE and becomes active after hydrolysis to EE (Fig. 2). As this transformation occurs rapidly, after intake in the intestinal tract and the liver, the pharmacokinetics of ME is similar to that of EE. Some other derivatives of EE, e.g., the 3-cyclopentylether (Quinestrol) or the 3-isopropylsulfonic acid ester (Ethinylestradiolsulfonate) which exert a depot-effect, are used in combination with a progestogen in the so-called once-a-month pill or once-a-week pill, respectively. These compounds also become active after hydrolysis to EE (Fig. 2).

EE is used in OCs, because it is also very potent after oral application and can be used at very low doses. The high potency is based on the ethinyl group at C17α which blocks the oxidative inactivation of estradiol into estrone. The binding affinity of EE for the estrogen receptor is similar to that of estradiol. After oral application, the bioavailability of EE is 38–48%, and the peak serum concentrations of EE are reached within 1–3 h. During daily intake, the EE levels increase up to a steady state which is reached after about 1 week. At a

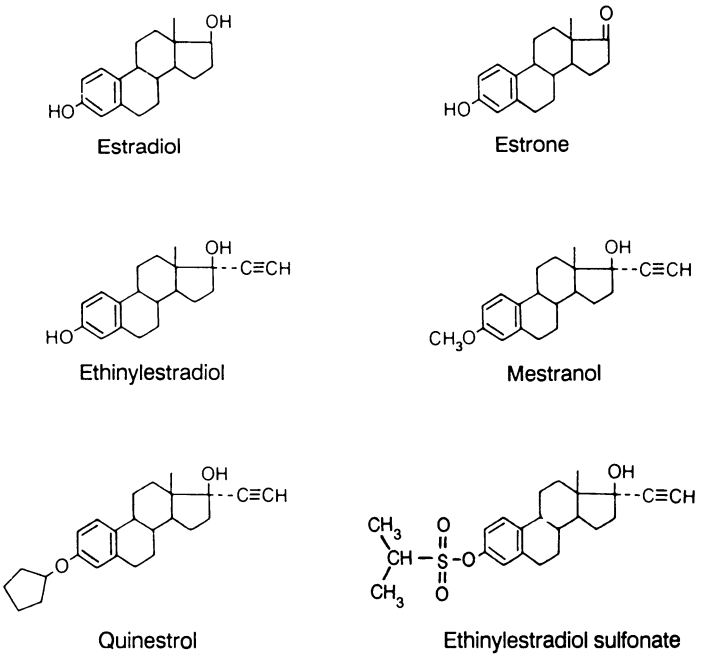

Fig. 2. Structural formulae of estrogens

dose of 30 μg, the maximal serum levels of EE are 100 pg/ml, and with 50 μg, a level of 150 pg/ml may be reached, on average. There are large intra- and interindividual variations both in the EE levels and in the physiological response during treatment with the same EE dose. In the serum, EE which has no affinity for sex hormone-binding globulin (SHBG) is bound to albumin.

EE has a proliferative effect on the epithelium of endometrium, tubes, vagina and urethra, and stimulates the production of cervical mucus. In the breast, it promotes ductal proliferation and alveolar branching. EE causes vasodilation and increases blood flow, stimulates collagen synthesis and water retention and inhibits bone resorption and gonadotropin release. It stimulates hepatic protein synthesis and causes alterations of numerous metabolic serum parameters. The effects of EE are dose-dependent; even at a dose as low as 5 μg, EE may change several serum parameters, but at doses above 20 μg, the increments become continuously smaller (MASHCHAK et al. 1982; MANDEL et al. 1982). Although the hepatic effect of EE is much stronger than that of estradiol, its proliferative effect on the endometrium is less than that of the natural estrogen (BROSENS and PIJNENBORG 1976), provided that no progestogen is present.

II. Pharmacology of Progestogens

The two types of progestogens used in OCs, are the derivatives of progesterone and of 19-nortestosterone. Those compounds which do not possess a 4-ene-3-keto group, represent pro-drugs, which are rapidly transformed in the intestinal tract and the liver into the active progestogen (Fig. 3). The progestogens used in OCs represent potent antagonists of EE that inhibit estrogen-induced proliferation and cause secretory transformation of the endometrium. They increase basal temperature by about 0.5°C and reduce tubal motility and cervical mucus even at low doses. According to their pharmacological properties, the progestogens may influence hepatic metabolism and may counteract the effects of EE. As the various progestogens may bind not only to the progesterone receptor, but also to a different extent to the androgen, glucocorticoid and mineralocorticoid receptor, they may exert some androgenic, anti-androgenic, glucocorticoid or anti-mineralocorticoid effects (Table 3). Therefore, the dose and hormonal pattern of the various progestogens and, consequently, the resulting effects of the combination with different doses of EE determine the tolerability and susceptibility of an individual woman to adverse effects.

Within 1–3 h after intake, the peak serum levels of the active progestogens are reached, which increase during daily intake up to a steady state (KUHL 1990a; STANCZYK 1997). In the serum, most of the nortestosterone derivatives are bound with high affinity/low capacity to SHBG and with low affinity/high capacity to albumin, while the remaining compounds and the progesterone derivatives are bound only to albumin. Similar to EE, the serum levels of the progestogens show large intra- and interindividual variations (KUHL 1990a).

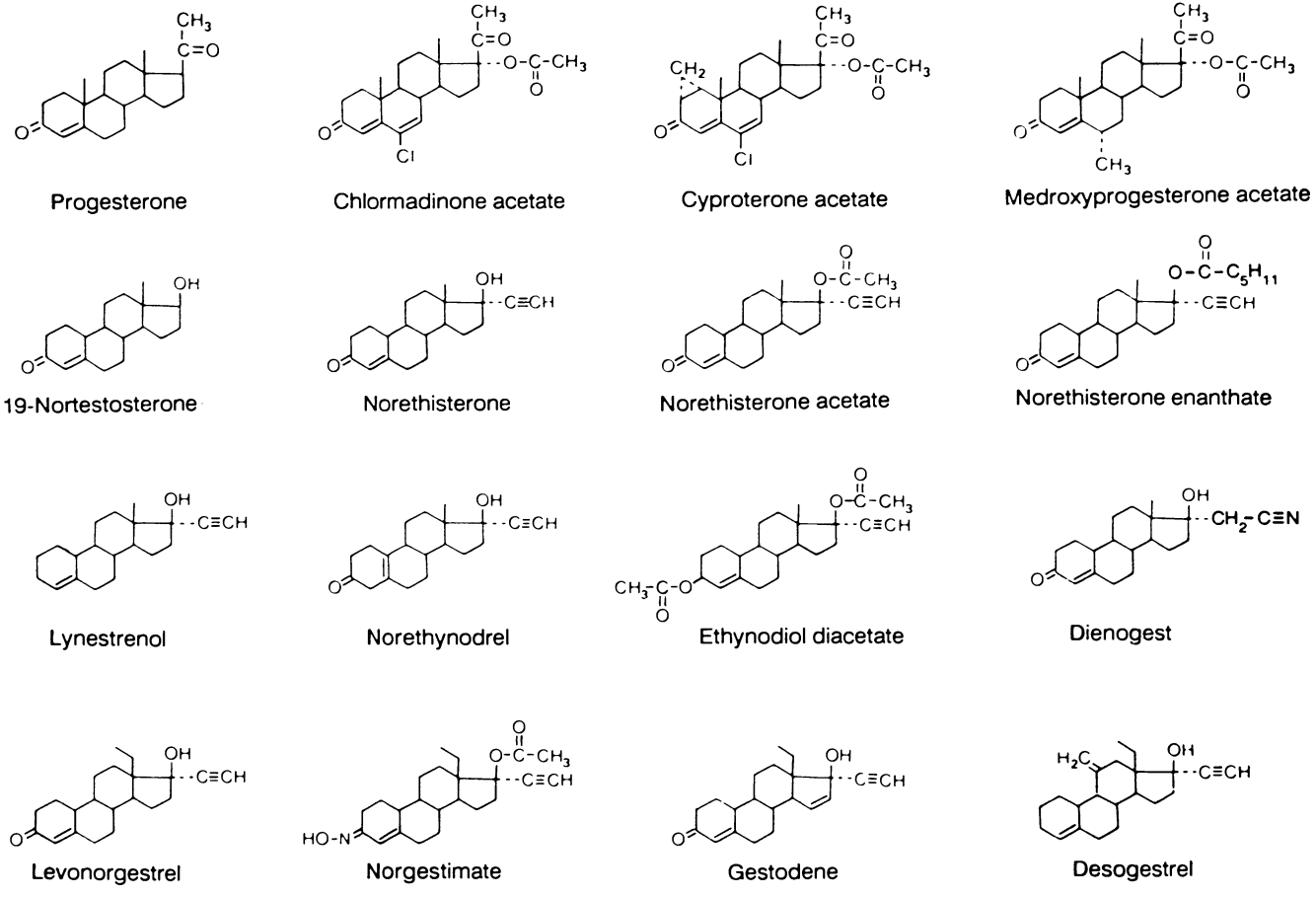

Fig. 3. Structural formulae of progestogens

Table 3. Spectrum of hormonal effects of progestogens (mostly evaluated by animal experiments)

Progestogen	E	AE	A	AA	GC	AMC
Progesterone	–	+	–	(+)	(+)	+
Chlormadinone acetate	–	+	–	+	+	–
Cyproterone acetate	–	+	–	+	+	–
Medroxyprogesterone acetate	–	+	(+)	–	+	–
Dienogest	–	+	–	+	–	–
Norethisterone	(+)	+	+	–	–	–
Norethisterone acetate	(+)	+	+	–	–	–
Lynestrenol	(+)	+	+	–	–	–
Ethynodiol diacetate	(+)	+	+	–	–	–
Norethynodrel	+	+	+	–	–	–
Levonorgestrel	–	+	+	–	–	–
Norgestimate	–	+	+	–		
Desogestrel (DG)	–	+	+	–		–
Gestodene (GSD)	–	+	+	–	(+)	+

E, estrogenic; AE, anti-estrogenic; A, androgenic; AA, anti-androgenic; GC, glucocorticoid; AMC, anti-mineralocorticoid effect

1. Nortestosterone Derivatives

The high oral potency of nortestosterone derivatives depends on the ethinyl group at C17α which may inhibit enzymatic inactivation of the steroid hormones by reductases and monooxidases. Therefore, this type of progestogen, which possesses some androgenic properties, exerts a pronounced effect on hepatic metabolism. The nortestosterone derivatives can be divided into two subgroups. The estranes (13-methyl-gonanes) comprise of norethisterone (NET), lynestrenol (LYN), ethynodiol diacetate (ETY) and norethynodrel (NYD) (Fig. 3). NET was the first orally active progestogen used for hormonal contraception, while LYN, ETY and NYD are pro-drugs, which become active after transformation into NET (KUHL 1990a). The so-called gonanes (13-ethyl-gonanes) include LNG, desogestrel (DG), norgestimate (NGM), and gestodene (GSD) (Fig. 3). The introduction of the ethyl group at C13 instead of a methyl group led to a pronounced enhancement of hormonal potency, as exemplified by NET and LNG (Table 2). Norgestrel, which consists of LNG and the hormonal inactive stereoisomer dextronorgestrel (1:1), is still used in some older formulations (STANCZYK and ROY 1990). A special position is occupied by dienogest (DNG), which belongs to the nortestosterone derivatives, but has no ethinyl group and no androgenic, but even anti-androgenic, properties. As DNG has a short half-life, the daily dosage must be higher than that of the other nortestosterone derivatives (KUHL 1996a).

DG and NGM are prodrugs which are transformed into 3-keto-DG and LNG, respectively. Except DG, NGM and DNG, nortestosterone derivatives including 3-keto-DG are bound to SHBG. The main metabolic pathways of

nortestosterone derivatives are the reduction of the 4-ene-3-keto group and hydroxylation reactions at various positions of the steroid.

The effects of the progestogens on different organs and tissues may diverge. This is exemplified by DNG which has a pronounced effect on the endometrium comparable with that of NGM or LNG. On the other hand, the ovulation-inhibiting potency of DNG is much less than that of NGM or LNG, and is comparable to that of progesterone derivatives (Table 2).

2. Progesterone Derivatives

As progesterone is rapidly inactivated after oral intake, it is not suitable for oral contraception. By introducing substituents, such as methyl or chloro groups, into the progesterone molecule, the reductive metabolism at ring A and at C20 is slowed down. The lack of an ethinyl group explains not only the lower hormonal potency of progesterone derivatives, but also their lower impact on hepatic metabolism. Among the progesterone derivatives, only chlormadinone acetate (CMA), cyproterone acetate (CPA) and medroxyprogesterone acetate (MPA) are used for hormonal contraception (Fig. 3). Due to their anti-androgenic properties, CMA and particularly CPA are used in OCs for treatment of androgenic symptoms, while MPA is used as a depot-progestogen.

D. Mode of Action of Oral Contraceptives

The high contraceptive efficiency of OCs is based on their profound influence on many target organs involved in the events leading to conception and pregnancy. The estrogen and progestogen component may act synergistically or antagonistically. The effect of the progestogen is largely dependent on the presence of a potent estrogen which induces the synthesis of the progesterone receptor. In contrast, in the endometrium and other organs, progestogens may reduce the binding capacity of estrogen receptors and may decrease the local estrogen concentration by enhancing degradation of estrogens.

The inhibition of ovulation is brought about by an early disturbance of the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion pattern and a direct interaction of EE and the respective progestogen with ovarian processes, which lead to an impairment of follicular development (Kuhl 1996a). If this mechanism was not sufficient for the prevention of follicular maturation, the pre-ovulatory LH surge and, hence, ovulation would be prevented by the progestogen component. In most women, the reduction in gonadotropin release results in a suppression of ovarian estradiol and testosterone production. In a certain proportion of women, follicular maturation begins during the hormone-free week and continues during the first days of pill intake (Kuhl et al. 1985b). In these women, relatively high serum levels of estradiol can be measured, even though ovulation is reliably suppressed,

provided that no omission of tablets has occurred. As follicular development may start during the pill-free week, the first week of pill intake is the most crucial period of time with respect to contraceptive effectiveness. The risk of ovulation and undesired pregnancy is highest, if omission of tablets occurs during the first week of the pill cycle, i.e., if the hormone-free interval is prolonged. Even though, in a normal 28-day cycle, ovulation occurs around day 15, on average, in a certain proportion of women it may take place some days earlier.

Both EE and the synthetic progestogen may impair tubal function, transport of the zygote, composition of tubal secrets and endometrial function, the changes of which are synchronized by the cyclic course of endogenous estradiol and progesterone levels. Using combination formulations, the early action of the progestogens inhibits estrogen-dependent proliferation of the endometrium and causes premature secretory transformation, resulting in an endometrium which is not receptive for implantation. The progestogen also counteracts the effect of the estrogen on cervical mucus and impairs penetration and ascension of sperms. With respect to the effects on the endometrium and cervix, the effect of the progestogen component overweighs that of the estrogen.

In addition to its contribution to the contraceptive effect, the estrogen component plays an important role in the maintenance of regular bleeding. In the presence of a potent progestogen, the intracellular inactivation of estradiol in the endometrium is profoundly enhanced. Therefore, the use of estradiol in oral contraceptives is associated with a high rate of inter-menstrual bleeding. In contrast, EE which is resistant to the action of the 17β-hydroxysteroid dehydrogenase, shows a sufficient endometrial activity and allows relatively stable cycles when combined with potent progestogens.

On the other hand, EE is a potent estrogen which may alter hepatic metabolism and cause changes in many metabolic parameters. In predisposed women, this impact may lead to the development of metabolic disturbances and various diseases.

E. Pharmacokinetics of Oral Contraceptives

I. Factors Influencing Efficacy

The effectiveness of OCs depends on sufficiently high serum concentrations of EE and the respective progestogen. Although there are large inter-individual variations in the serum levels of the synthetic sex steroids, the dosages are sufficient for all women. The levels are not dependent on body weight, but primarily on the metabolic capacity of the intestinal tract and liver. Therefore, the inter-individual differences in the EE and progestogen levels are due to genetic or acquired predisposition. There are also large intra-individual variations from day to day, which may be caused by diet, drugs or environmental factors (JUNG-HOFFMANN and KUHL 1990).

During treatment with OCs, the maximal serum concentrations are reached within 1–4 h after intake of the tablet; thereafter, a rapid decline of the serum levels can be observed. During the phase of elimination, the serum concentration of EE is also influenced by the enterohepatic circulation; a certain proportion of EE-conjugates is split by the bacterial flora in the colon, and the reabsorbed EE contributes to the circulating EE. This does not hold true for the progestogens, as their metabolites are hormonally inactive.

The absorption of EE and the progestogens in the small bowel is completed within 2–3 h after intake of a tablet. Therefore, vomiting may impair contraceptive efficacy but only during the first 2–3 h after ingestion. A possible influence of diarrhea depends on the severity of the disease. Generally, only the colon is affected, and this may impair only the enterohepatic circulation of EE. As this mechanism does not concern the progestogen, diarrhea usually does not influence the contraceptive action of formulations with a potent progestogen component, but may cause inter-menstrual bleeding. It should, however, be kept in mind that nausea and illness may lead to an omission of tablets.

In general, the effectiveness of OCs is not impaired in women with inflammatory bowel diseases, e.g., ulcerative colitis, Crohn's disease, cystic fibrosis or celiac disease. While diet may influence the pharmacokinetics of contraceptive steroids, no significant effect of smoking could be demonstrated. Chronic alcohol abuse, but not short-term alcohol drinking, may reduce the contraceptive efficacy of OCs.

II. Interaction of Oral Contraceptives with Drugs

There are numerous reports of irregular bleeding and undesired pregnancies in women who were concomitantly treated with OCs and certain drugs (Back et al. 1988; Szoka and Edgren 1988; Back and Orme 1990). Although in many cases a causal relationship is improbable, an interaction cannot be excluded with certainty, as there are large inter-individual variations in the serum levels of sex steroids and in the metabolic response to treatment with OCs and drugs. A possible interaction with the pharmacokinetics of contraceptive steroids has been investigated only for some drugs, and mostly in small groups of volunteers. As women with chronic diseases often need a lifelong therapy, and as some of the drugs are potentially teratogenic, the knowledge of possible interferences with the contraceptive reliability of OCs is essential.

There are two main pathways leading to a decrease in the serum levels of contraceptive steroids. An enzyme induction induced by drugs may cause an enhancement of hepatic metabolism of both EE and the progestogens. The most important enzyme inducers that may impair efficiency of OCs are rifampicine, griseofulvine, anti-epileptics such as phenobarbital, phenytoin. primidone, carbamazepine and oxcarbazepine, and several other tranquilizers (Table 4). An interruption of the enterohepatic circulation of EE by antibiotics may reduce EE, but not progestogen levels. The latter may be of importance

Table 4. Interaction of drugs with the effectiveness of oral contraceptives

Drug	Effectiveness
Antibiotics, sulphonamides	
Rifampicin	RP, EM
Isoniazid	RP %
Ampicillin	RP
Phenoxymethylpenicillin	RP
Oxacillin	RP
Amoxicillin	RP
Tetracycline	RP
Cotrimoxazole	(RP), IM
Cefalexin	RP, (EM)
Chloramphenicol	RP
Neomycin	RP
Eythromycin	(RP), (IM)
Fusidic acid	RP
Sulphamethoxazole	RP
Sulphmethoxypyridazine	RP
Sulfisoxazole	RP
Dapsone	(RP), IM
Nitrofurantoin	RP
Metronidazole	RP
Clarithromycin	%
Roxithromycin	%
Doxycycline	%
Temafloxazin	%
Ciprofloxazin	%
Dirithromycin	EM
Triacetyloleandomycin	IM
Primaquine	%
Chloroquine	%
Ofloxacin	%
Vitamins	
Vitamin C	%
Isotretinoin	%
Tretinoin derivatives	%
Anti-epileptics	
Phenobarbital	RP, EM
Methylphenobarbital	RP, EM
Primidone	RP, EM
Phenytoin	RP, EM
Carbamazepine	RP, EM
Ethosuximide	(RP) %
Methosuximide	RP
Sodium valproate	(RP) %
Oxcarbazepine	%
Analgesics, anti-inflammatory agents	
Phenylbutazone	RP, EM
Oxyphenbutazone	RP
Aspirin	RP
Phenazone (Anti-pyrine)	RP
Aminophenazone	RP
Phenacetin	RP

Table 4. (*Continued*)

Drug	Effectiveness
Aminopyrine	RP
Paracetamol	(RP), %
Ibuprofen	%
Anti-histamines, H2-Antagonists	
Cimetidine	%
Roxatidine	%
Ranitidine	%
Diphenhydramine	(EM)
Adsorbents, antacids	
Aluminium hydroxide	%
Magnesium trisilicate	%
Kaolin	%
Activated charcoal	%
Tranquillisers, neuroleptics, sedatives	
Barbital	RP, EM
Phenobarbital	RP, EM
Promethazine	RP, EM
Chlorpromazine	RP, EM
Diazepam (Valium)	RP, EM
Chlordiazepoxide	RP, EM
Clorazepate	RP, EM
Meprobamate	RP, EM
Triflupromazine	(EM)
Prazepam	EM
Alprazolam	EM
Nordazepam	EM
Temazepam	EM
Oxazepam	%
Lorazepam	%
Diphenhydramine	(EM)
Anti-depressants	
Imipramine	(EM)
Tolbutamide	%
Carbutamide	%
Antidiabetic agents	
Tolbutamide	%
Carbutamide	%
Immunosuppressants	
Cyclosporin	IM
Anti-fungal agents	
Griseofulvin	RP, EM
Ketoconazole	IM
Terbinafine	IM
Diuretics	
Metyrapone	(IM)

RP, reported pregnancies; EM, enhancement of metabolism and attenuation of efficacy; IM, inhibition of metabolism and enhancement of efficacy; %, no influence on hepatic metabolism of contraceptive steroids

when OC formulations are used that contain a less potent progestogen component, or a very low or no progestogen dose during the first week of intake, e.g., triphasic or sequential OCs. The problem of antibiotic interaction is complicated by the fact that within several days of antibiotic therapy, resistant bacterial flora develops in the colon, which normalizes enterohepatic circulation. A large proportion of the population might already have an intestinal bacterial flora that is resistant to the commonly used antibiotics. There are some drugs that may modulate conjugation and metabolism of steroids in the small bowel, and there are others that may inhibit hepatic metabolism and, hence, enhance the effects and side effects of OCs (Table 4).

However, OCs may alter the effects of drugs by inhibition of drug metabolism, or by enhancing conjugation of drugs. As the therapeutic window of most drugs is large, this effect is of minor clinical relevance. It has, however, been shown that OCs may considerably increase the extent of side effects of imipramine due to the action of EE. The estrogen component may also enhance the conjugation of some drugs and reduce their effectiveness. This is exemplified by the inhibition of warfarin metabolism and the enhancement of phenprocoumone conjugation (Table 5). In such cases, the effectiveness of the drugs may be adapted by changing the drug dose.

Table 5. Interaction of oral contraceptives with the efficacy of drugs

Drug	Efficacy
Antibiotics	
Ampicillin	%
Tetracycline	%
Metronidazole	%
Isoniazid	%
Triacetyloleandomycin	IM
Quinine	%
Mefloquine	%
Analgesics, anti-inflammtory agents	
Phenylbutazone	IM
Phenazone (Anti-pyrine)	IM
Aminopyrine	IM
Metamizol	IM
Phenacetin	IM
Meperidine (Pethidine)	IM
Paracetamol	EC
Diflunisal	EC
Aspirin	EC
Salicylic acid	EC
Morphine	EC
Ethylmorphine	IM
Corticosteroids	
Cortisol	IM
Prednisolone	IM
Fluocortolone	%

Table 5. (*Continued*)

Drug	Efficacy
Tranquilizers, neuroleptics, sedatives	
Diazepam	IM
Alprazolam	IM
Triazolam	IM
Nitrazepam	IM
Chlordiazepoxide	IM
Bromazepam	%
Clotiazepam	%
Lorazepam	EC
Temazepam	EC
Midazolam	%
Doxylamine	%
Diphenhydramine	%
Anti-arrhythmic agents, β-adrenoceptor blocking agents	
Chinidine	(IM)
Lidocaine	(IM)
Propranolol	IM,EC
Oxprenolol	(IM)
Metoprolol	(IM)
Calcium antagonists, cardiac inotropic agents	
Nifedipine	(IM)
Digitoxin	(IM)
Anti-epileptics	
Phenytoin	IM
Anti-depressants	
Imipramine	IM
Clomipramine	%
Xanthines	
Caffeine	IM
Theophylline	IM
Immunosuppressants	
Cyclosporin	IM
Anti-coagulants	
Warfarin	IM
Phenprocoumon	EC
Anti-diabetic agents	
Tolbutamide	IM
H_2-Antagonists	
Cimetidine	%
Doxylamine	%
Lansoprazol	%
Diphenhydramin	%
Vitamins	
Vitamin A	IM
Lipid regulating agents	
Clofibrate	EC

IM, inhibition of metabolism and enhancement of efficacy; EC, enhancement of conjugation and attenuation of efficacy; %, no influence on metabolism of drugs

F. Use of Oral Contraceptives

I. Choice of Oral Contraceptives

Before an OC is prescribed, an internal and gynecological examination must be carried out. A careful anamnesis and family history may help to recognize risks or predisposition for the development of thromboembolic or other diseases. Possible absolute and relative contraindications must be taken into consideration (Table 6). Hormone determinations are worthless except in women

Table 6. Absolute and relative contraindications to the use of oral contraceptives

Absolute contraindications
Acute and chronic progressive liver disease
Impairment of bile secretion, cholestatic jaundice (also a history of)
Hemolytic uremic syndrome
Previous or current thrombo-embolic disease (venous thrombosis, stroke, myocardial infarction)
Micro- or macroangiopathia
Hereditary thrombophilia
Lupus erythematosus
Vasculitis
Anti-phospholipid antibodies
Circulatory disorders
Severe hypertension
Diabetes mellitus with angiopathia
Hyperhomocysteinemia
Severe hypertriglyceridemia
Breast cancer
Undiagnosed vaginal bleeding
Pregnancy
Relative contraindications
Liver disease (e.g., porphyria)
Gall-bladder disease
Disorders of lipid metabolism
Diabetes mellitus
Disorders of hemostasis
Vascular lesions
Cardiac or renal dysfunction, edema
Cardiac surgery
Angina pectoris
Previous or current thrombophlebitis
Smoking
Hypertension
Obesity
Lactation
Mastopathia with epithelial atypia
Uterine myoma
Elective surgery with major thrombo-embolic risk
Long-term immobilization
Endometrial cancer
Cervical cancer
Migraine

with androgenic symptoms. Biochemical laboratory parameters should be measured only when indicated. First time users should be reassessed after 3–4 months of use. Thereafter, monitoring is necessary only every 12 months and, in the case of any risk factors, every 6 months. During monitoring, it is important to look for the onset of new risk factors or warning signs. Regular measurement of blood pressure, cervical cytology and breast examination is recommended.

The choice of the formulation depends on the individual disposition and situation. As most side effects are dependent on the EE dose, a low-dose combination formulation should be prescribed for first-time users, i.e., preparations containing 35 μg EE or less. The doses of the various progestogens cannot be compared with respect to the metabolic impact, as their potencies differ largely. A comparison of the dose used with the ovulation-inhibition dose of the respective progestogen may give a reference point for efficacy. Oral contraception should be started on the first day of menses in order to increase contraceptive effectiveness. Thereafter, the pills must be taken according to instructions for 21–22 days, followed by a hormone-free interval of 6–7 days. During this time, withdrawal bleeding takes place. The next package of pills should be started immediately after this time. In preparations with 28 pills, the last seven tablets contain a placebo in order to facilitate correct use.

Omission of tablets may impair contraceptive efficacy and lead to undesired pregnancies, particularly during the first week of intake. If one tablet is missed, the woman should take that pill as soon as possible and take the following tablet as usual. If two tablets are missed, two pills on each of the following 2 days should be taken. If more than two tablets are missed, alternative contraceptive measures, e.g., condom or diaphragm plus spermicides, should be used additionally.

It is important to inform the patient of the possible occurrence of intermenstrual bleeding and other side effects which may occur more frequently during the first treatment cycles. If, thereafter, side effects continue and cannot be tolerated, change to another preparation should be taken into consideration. In the case of certain symptoms indicating serious diseases, pill intake must be stopped immediately (Table 7).

II. Metabolic Effects of Oral Contraceptives

OCs may exert a pronounced influence on many metabolic and clinical laboratory parameters. In most cases, the estrogen component acts in a stimulatory manner, i.e., it increases the serum concentrations of most parameters, while the progestogen components show mostly a modulatory or antagonistic effect. In general, the effects are dose- and time-dependent. Some of the alterations induced by OCs are highest during the first weeks of intake and are attenuated during long-term treatment, while other parameters increase continuously during several months before reaching a steady state. Therefore, the estimation of long-term effects and risks, on the basis of the results of short-term studies, might be questionable.

Table 7. Reasons for immediate discontinuation of oral contraceptives

Pregnancy
First-time occurrence or aggravation of migraine or severe headaches
Transient cerebral attacks (e.g., speech disorder, numb feeling)
Acute blurred vision
Severe pain in the chest which increases at breathing (myocardial infarction)
Unilateral severe leg pain (thrombosis)
Pain in the chest, unclear difficulty of breathing, hemoptysis (pulmonary embolism)
Thrombophlebitis
Cholestatic jaundice
Epigastric pain (liver disease, gall-stones, thrombosis)
Marked rise of blood pressure
Severe generalized cutaneous eruption (erythema multiforme)
Growth of existing uterine myoma
4–6 Weeks before an elective surgery
Long-term immobilization (e.g., after an accident)

1. The Liver

Orally taken estrogens and progestogens exert a considerably stronger effect on the liver than parenterally applied sex steroids. This is due to the high steroid concentration of serum during the first liver passage, which is about 4-fold that of the peripheral levels (BACK et al. 1982). The liver also differs from other organs, as the higher permeability of hepatic vascular beds and the larger surface area of the liver's microvasculature cause a stronger influx of sex steroids than other organs (STEINGOLD et al. 1986). Binding to albumin, which is the only carrier of EE in serum, does not or only marginally influence uptake of the synthetic estrogens by hepatocytes (STEINGOLD et al. 1986). Moreover, synthetic sex steroids used in OCs elicit a much stronger effect on hepatic metabolism than natural sex steroids, as their inactivation is retarded and the local concentration in the hepatocytes is probably higher. Among the progestogens, nortestosterone derivatives containing an ethinyl group probably have a more pronounced impact on hepatic metabolism than dienogest and progesterone derivatives. Therefore, the effect of OCs on hepatic factors is much more pronounced than that on non-hepatic parameters, and the ratio between hepatic and peripheral activity of EE is much higher than that of natural estrogens (MASHCHAK et al. 1982).

The liver is one of the most important target organs of estrogens, which not only affect the synthesis and activity of many enzymes and other proteins, but may also alter the composition of gall-bladder bile and impair the transport of biliary components. The EE component increases biliary concentration of cholesterol and cholic acid and reduces that of deoxycholic acid and chenodeoxycholic acid. In predisposed women, this may lead to gall-bladder disease, intra-hepatic cholestasis, jaundice and pruritus during treatment with OCs.

During the first three cycles of treatment with high-dose OCs, a transitory rise of various liver function parameters may occur, e.g., of aspartate amino-

transferase (ASAT), alanin aminotransferase (ALAT), γ-glutamyltransferase (γ-GT), glutamate dehydrogenase, or β-glucuronidase. Such effects are rarely observed when low-dose OCs are used. A decrease in the activity of alkaline phosphatase and cholinesterase and an increase in lactate dehydrogenase can, however, be measured also when low-dose OCs are used. In general, alterations of liver function parameters remain in the normal range and are reversed after some treatment cycles. Therefore, screening of liver function is justified only on suspicion of liver disease or a past history of these diseases.

2. Lipid Metabolism

Due to their strong hepatic effect, EE and – to a different extent – the progestogens may alter lipid metabolism. The estrogen increases the synthesis of triglycerides (TG), apolipoproteins A and B, and high-density lipoprotein (HDL); it also stimulates the receptor-mediated uptake of remnants and low-density lipoprotein (LDL) in the liver and inhibits hepatic lipoprotein lipase (Krauss and Burkman 1992). Moreover, EE increases the proportion of unsaturated fatty acids and lecithin in phospholipids. Progestogens, particularly those with androgenic properties, may counteract the estrogen-induced effects by reducing TG synthesis and increasing the activity of hepatic lipoprotein lipase and the clearance of TGs.

Therefore, according to the composition of the OC, treatment with estrogen-dominant formulations results in a rise of HDL-cholesterol (HDL-CH), very low density lipoprotein (VLDL) and total TG, while LDL-CH remains unchanged (Kuhl et al. 1990b). The levels of lipoprotein (a) are reduced during treatment with OCs (Kuhl et al. 1993). The estrogen-induced rise in TG cannot be regarded as being deleterious, as it is not the result of a disturbed lipolysis, but is caused by an elevated synthesis of VLDL. At the same time, the hepatic elimination of LDL and TG-rich remnants is enhanced, which leads to a shortening of the residence time of atherogenic lipoproteins in the circulation. It has been suggested that the anti-oxidative effect of EE prevents LDL oxidation and accumulation in the arterial wall. Moreover, estrogens show a vasodilatory effect on the arteries and inhibit proliferation of smooth muscle cells. Therefore, even during use of OCs, which may change lipid metabolism in an unfavorable manner, there seems to be no acceleration of the development of atherosclerosis. The increased risk of myocardial infarction in pill users who smoke, may be due to the occurrence of vasospasms in atherosclerotic coronary arteries, which might be triggered by the vasoconstrictory action of the progestogen component. In these cases, the manifestation of an ischemic cardiovascular disease may also be facilitated by the pro-coagulatory action of OCs.

In women with hyperlipoproteinemia type II or III, OCs are contraindicated if vascular lesions have developed. If no additional risk factors are present, OCs may be used (Knopp et al. 1993). In women with hypertriglyceridemia, due to an impaired lipolysis (type VI or V), OCs are contraindicated.

3. Renin-Angiotensin-Aldosterone System (RAA System)

Due to the strong influence of EE on the liver, OCs may increase the serum concentration of angiotensinogen 3- to 5-fold which, after discontinuation of treatment, is rapidly reversed (DERKX et al. 1986). Although the renal release of renin is reduced, the high renin substrate level leads to an enhanced production of angiotensin I which is transformed by the angiotensin converting enzyme (ACE) to angiotensin II. The 2- to 3-fold increase in angiotensin II causes a corresponding rise in aldosterone secretion which reduces the release of renin by 50%. The EE-induced increase in renin activity which is dose-dependent, is less pronounced during treatment with low-dose OCs (DERKX et al. 1986) While aldosterone may increase the retention of sodium and water and cause the development of edema, the elevated angiotensin-II levels may contribute to a slight increase in blood pressure. There is, however, no correlation between the alterations of blood pressure and plasma concentrations of renin, angiotensin II or aldosterone, or plasma volume (WEIR et al. 1975). The changes observed during treatment with OCs are similar in normotensive and hypertensive women. Therefore, the development of hypertension is not directly caused by the stimulation of the RAA system. In contrast to OCs, no influence of progestogen-only preparations on RAA system is observed.

4. Carbohydrate Metabolism

Low-dose OCs have only a marginal influence on fasting glucose levels, but may cause a slight hyperinsulinemia. This is the result of a decrease in insulin sensitivity, which is caused by a synergistic action of EE and the progestogen. The elevated C-peptide levels indicate an enhancement of both the secretion and clearance of insulin. Long-term treatment with OCs is associated with a slight insulin resistance and impairment of glucose tolerance which is compensated by the rise in insulin levels (CROOK et al. 1988; KRAUSS and BURKMAN 1992; GODSLAND and CROOK 1994). There is, however, no change in the levels of glycated proteins or HbA1. The glucagon levels are increased by EE and decreased by progestogens, and the resulting effect is dependent on the composition of the OC.

In most women, the changes in carbohydrate metabolism are reversible and are without clinical relevance; only in predisposed women, i.e., in 4–5% of OC users, are pathological alterations observed. In women with impaired glucose tolerance, OCs may cause a slight deterioration which may be enhanced during long-term treatment (Wynn 1982). The progression of a disturbed glucose tolerance to a manifest diabetes mellitus is, however, independent of OC treatment. Therefore, there is no significant influence of OCs on the incidence of non-insulin-dependent diabetes mellitus (NIDDM, type II) (RIMM et al. 1992). In women with diabetes mellitus, treatment with OCs might, however, increase the risk of cardiovascular diseases. The role of an OC-induced increase in the serum levels of growth hormone and TG is not yet clarified.

5. Hemostasis

Due to the marked action of EE on the liver, there is a rise of many coagulation and fibrinolysis factors. Progestogens, particularly those with androgenic properties, may slightly antagonize these effects (KUHL 1996b). During treatment with OCs, an increase in the serum levels of fibrinogen, Willebrand factor, prothrombin, and factors VII, VIII, IX, X, and XII can be observed (COHEN et al. 1988; BALL et al. 1990; DALY and BONNAR 1990; PETERSEN et al. 1993; TAUBERT and KUHL 1995). While there is a decrease in antithrombin-III activity, Protein C is increased and protein S mostly unchanged. The enhancement of fibrinolytic activity is mainly based on the rise of the plasminogen level and the activity of tissue-plasminogen activator (t-PA). The elevated turnover of fibrin is reflected by a marked increase in the serum levels of fibrinopeptide A, fragments 1 + 2, fibrin monomers, D-Dimer and fibrin degradation products. The changes of the various clotting and fibrinolytic factors induced by EE are time- and dose-dependent, but there are differences between the various factors with respect to the time-course and extent of changes. During OC use, a steady state of the hemostasis/fibrinolysis system at a higher level is reached within a few weeks. After termination of treatment, the return to baseline of the altered concentrations and activities of hemostasis factors which have varying half-lives, needs different periods of time.

Although the rise in coagulation factors is generally compensated by the increase in fibrinolytic activity, the hypercoagulable state induced by OCs may contribute to the development of thromboembolic diseases in predisposed women. The risk of deep vein thromboses and pulmonary emboli is particularly increased in women with resistance to activated protein C (APC), or with a deficiency of anti-thrombin III, protein C or protein S. Recent investigations indicate that OCs may impair the effect of activated protein C and induce APC-resistance (OLIVIERI et al. 1996; ROSING et al. 1997).

The development of venous thromboses is a local phenomenon. As the activation of the coagulation cascade is triggered by the interaction of thrombocytes and endothelium, it appears probable that OCs may influence these local mechanisms. It is known that OCs may influence platelet aggregation and the metabolic activity of the endothelium.

6. Serum Proteins

According to their composition, oral contraceptives may alter the serum levels of various hepatic proteins, particularly serum binding globulins. These binding proteins play a role in the regulation of various hormones including sex steroids. It is assumed that only the free proportion of a hormone may be bound at the cell membrane or penetrate through the membrane, while the protein-bound hormone is hormonally inert and may serve as a circulating reservoir. This may particularly hold true for the role of serum binding globulins, which may bind sex steroids, corticosteroids or thyroid hormones with high affinity and may influence the biological activity of the hormones.

Treatment with EE increases dose-dependently the serum concentrations of SHBG, corticosteroid-binding globulin (CBG) and thyroxine-binding globulin (TBG).

In post-menopausal women, a dose of only 5 μg EE increases SHBG levels by 100% and a dose of 20 μg EE by 200% (MANDEL et al. 1982). While progesterone derivatives do not influence SHBG, nortestosterone derivatives may decrease SHBG levels according to their androgenic properties. Therefore, the composition of the OC is crucial to the resulting effect of the formulation: treatment with 20 μg EE + 250 g LNG reduces SHBG by 50%; 30 μg EE + 250 μg LNG has no influence; 30 μg EE + 150 μg LNG increases SHBG by 30%, and the EE/LNG containing triphasic OC causes a rise in SHBG by 100–150%. The combination of 30 μg EE with 150 μg DG increases SHBG levels by 200% and 35 μg EE + 2 mg cyproterone acetate by 400%. An excessive EE-induced rise in serum SHBG is, however, not associated with a corresponding decrease in free testosterone (JUNG-HOFFMANN and KUHL 1987; VAN DER VANGE et al. 1990).

CBG responds to a lesser extent than SHBG to treatment with EE. In post-menopausal women, a dose of 10 μg EE increases CBG levels by 50% and 20 μg EE by 100% (MANDEL et al. 1982). Progesterone derivatives have no effect and nortestosterone derivatives only a weak effect on CBG. Therefore, treatment with low dose OCs may cause a rise in CBG by 100–150% (VAN DER VANGE et al. 1990).

In post-menopausal women, 5 μg EE increase TBG by 40% and 20 μg EE by 60%. Progesterone derivatives do not influence TBG, while nortestosterone derivatives with androgenic properties may antagonize the estrogen-induced rise. During treatment with 30 μg EE + 1 mg NET, TBG levels rise by 50–70%, and with 30 μg EE + 150 μg DG by 100%.

OCs do not or only marginally affect the serum levels of albumin or total protein. The EE component of OCs causes a rapid increase in the serum concentrations of transferrin, ferritin and ceruloplasmin, while haptoglobin is reduced. In many women, a rise in C-reactive protein and a transitory increase in α-fetoprotein is observed during treatment with OCs. Immunglobulins A, G and M may be slightly elevated by OCs, while α1- and α2-globulin may increase and β-globulin decrease.

7. Hormones

Intake of OCs leads to a time-dependent decrease in FSH and LH secretion and, consequently, to a suppression of ovarian steroid synthesis. Therefore, the serum levels of estradiol are suppressed, whereby a direct inhibition of ovarian steroid production by EE and the synthetic progestogen might play a role. In a certain proportion of women, follicular maturation begins during the hormone-free interval of 7 days and may continue during the first week of OC intake, resulting in elevated estradiol levels. In the case of profound suppression of endogenous estradiol, no symptoms of estrogen deficiency occur, as the

EE levels are sufficient for replacement. OC treatment leads to a decrease in 17α-hydroxyprogesterone by 70–80% and in DHEA-S by 30–50% (KUHL et al. 1985b; JUNG-HOFFMANN et al. 1988) which reflects an inhibition of adrenal steroid synthesis, presumably by a direct interaction of ethinylated steroids (FERN et al. 1978). Accordingly, adrenal testosterone and androstendione production is reduced by OC. The action of OC on both ovarian and adrenal steroid synthesis leads to a reduction in testosterone levels by 30%.

Treatment with OCs does not significantly influence insulin-like growth factor-1 (IGF-1) or its binding protein IGFBP-1, while the level of growth hormone is increased by the estrogen component by about 50%. As a result of a rise in CBG levels, clearance of cortisol is reduced. Consequently, the serum concentration of total cortisol is elevated. There is, however, also a slight increase in free cortisol. High-dose OCs may cause a rise in adrenocorticotropic hormone (ACTH), while low-dose OCs are less effective.

OCs do not or only slightly influence thyroid function: the EE-induced rise in TBG is associated with a significant increase in the serum concentrations of T3 and T4; there is, however, no change or only a marginal change in the level of TSH, free T3, free T4, and the effective thyroxine ratio (KUHL et al. 1985a; JUNG-HOFFMANN et al. 1988).

Treatment with OCs causes a rise in the serum levels of vasopressin, oxytocin and atrial natriuretic peptide (ANP) and a fall in those of somatostatin and cholecystokinin, while leptin, gastrin and the vasoactive intestinal peptide (VIP) are unaffected.

8. Other Biochemical Laboratory Parameters

The EE component of an OC causes a rapid increase in the levels of ferritin, transferrin and total iron-binding capacity, which leads to a rise in serum iron. Similarly, the increase in the serum level of copper is caused by the EE-induced increase in the copper-binding protein ceruloplasmin which may be antagonized by progestogens with androgenic properties. In general, treatment with OCs results in a rise of serum ceruloplasmin by 100–140%. Most of the electrolytes and trace elements are not altered, except for a reduction in magnesium and nickel, and a slight but significant increase in sodium (Table 8). The latter may be due to the EE-dependent rise in aldosterone and vasopressin. The levels of hemoglobin and hematocrit, erythrocyte count and platelet count are not altered. There is, however, an increase in blood viscosity. OCs do not alter homocysteine concentrations. During treatment with high-dose formulations, the levels of several amino acids, e.g., glutaminic acid, alanin, glycin, glutamin and taurin, may be reduced.

During treatment with OCs, the serum concentrations of vitamin A increase by 50%, whereby the rise in retinol is accompanied by a decrease in β-carotin, particularly in smokers. There is also an elevation of calcitriol levels. In some of the women who use OCs, the serum concentrations of vitamin B1, B2, B6 and B12 may be – mostly transitorily – reduced. No change occurs with

Table 8. Effect of low-dose oral contraceptives on various clinical chemical laboratory parameters

Blood sedimentation rate	Slightly increased
Hematocrit	Unchanged
Erythrocyte count	Unchanged
Leukocyte count	Slightly increased
Platelet count	Unchanged
Plasma volume	Increased
Blood viscosity	Increased
Hemoglobin	Unchanged
Total protein	Unchanged
Albumin	Unchanged
SHBG	Increased
CBG	Increased
TBG	Increased
α_2-Macroglobulin	Unchanged
α_1-Anti-trypsin	Increased
α-fetoprotein	Unchanged
C-Reactive protein	Increased
Orosomucoid	Unchanged
Haptoglobin	Reduced
Ceruloplasmin	Increased
Transferrin	Increased
Ferritin	Increased
Iron	Increased
Copper	Increased
Magnesium	Reduced
Zinc	Unchanged
Calcium	Unchanged
Nickel	Reduced
Manganese	Unchanged
Selenium	Unchanged
Mercury	Unchanged
Aluminium	Unchanged
Lead	Unchanged
Cadmium	Unchanged
Sodium	Increased
Oxytocin	Increased
Vasopressin	Increased
Angiotensin I and II	Increased
Growth hormone	Increased
IGF-1 (somatomedin)	Unchanged
Somatostatin	Reduced
Cholecystokinin	Reduced
Gastrin	Unchanged
Leptin	Unchanged
Melatonin	Unchanged
Vasoactive intestinal peptide	Unchanged
Atrial natriuretic peptide	Increased
ACTH	Unchanged
Cortisol	Increased
Aldosterone	Slightly increased
TSH	Unchanged
T_3	Increased
FT_3	Unchanged

Table 8. (*Continued*)

T_4	Increased
FT_4	Slightly increased
Effective thyroxine ratio	Slightly increased
Reverse trijodothyronine	Unchanged
Vitamin A	Increased
Vitamin B_1	Unchanged
Vitamin B_2	Unchanged
Vitamin B_6	Unchanged
Vitamin B_{12}	Reduced
Vitamin C	Unchanged
25-OH-Vitamin D_3	Unchanged
1,25-$(OH)_2$-Vitamin D_3	Increased
Vitamin E	Unchanged
Vitamin H	Unchanged
Vitamin K	Unchanged
Folic acid	Unchanged
Panthotenic acid	Unchanged
Lactate	Increased
Pyruvate	Unchanged
Free fatty acids	Unchanged
Uric acid	Slightly reduced
Creatinine	Increased
Bilirubin	Reduced
Alkaline phosphatase	Reduced
ASAT (SGOT)	(Increased)
ALAT (SGPT)	(Increased)
Gamma-GT	(Increased)
Glutamate dehydrogenase	(Increased)
Lactate dehydrogenase	(Increased)
β-glucuronidase	(Increased)
Cholinesterase	(Increased)
Xanthuric acid excretion	Increased
Sulfobromophthalein retention	Increased

ACTH, adrenocorticotropic hormone;TSH, thyroid stimulating hormone; SHBG, sex hormone-binding globulin; CBG, corticosteroid-binding globulin; TBG, thyroxine binding globulin; ASAT, aspartate aminotransferase; SGOT, serum glutamic oxaloacetic transferase; ALAT, alanine aminotransferase; SGPT, serum glutamic pyruvate transferase; GT, glutamyl transferase; IGF-1, insulin-like growth factor-1

respect to other vitamins or folic acid (Table 8). If there is an effect, the alteration is probably caused by the estrogen component. In the case of vitamin A and D, the increase is probably due to an elevated serum level of binding proteins.

III. Beneficial Effects of Oral Contraceptives

The use of OCs is not only associated with an increased risk of various diseases (Table 9), but also with many benefits (Mishell 1982) (Table 10). The

Table 9. Adverse effects of oral contraceptives; increase in the relative risk of various diseases

Disease	Relative risk
Cardiovascular diseases (total)	1.5
Myocardial infarction (total)	3.3
Myocardial infarction (non-smokers)	1.0
Myocardial infarction (light smokers)	3.5
Myocardial infarction (heavy smokers)	20.0
Cerebrovascular diseases (total)	1.4
Cerebral thromboses	2.5
Subarachnoidal bleeding (heavy smokers)	10.0
Pulmonary embolism	3.0
Deep venous thromboses	2.5
Gall-bladder diseases	3.0
Benign liver tumors	50.0
Hepatocellular carcinoma	3.0
Erythema nodosum et multiforme	3.0
Pruritus	2.0
Photosensitive eczema	4.0
Irritant agent eczema	2.0
Dermatitis	2.0
Chloasma	1.5
Cervicitis (6 years of use)	3.0
Chlamydial infections	2.5

Table 10. Beneficial effects of oral contraceptives; reduction in the relative risk of various disorders or diseases

Disorders or diseases	Relative risk
Iron-deficiency anemia	0.58
Menorrhagia	0.52
Irregular cycles	0.65
Inter-menstrual bleeding	0.72
Dysmenorrhea	0.37
Pelvic inflammatory disease	0.50
Benign breast disease	0.69
Rheumatoid arthritis	0.49
Endometrial cancer	0.50
Ovarian cancer	0.37

most important advantage of OC use is the significant reduction in the risk of ovarian cancer and endometrium cancer, benign breast disease and pelvic inflammatory disease. There are also less ovarian cysts, probably less uterine myoma and endometriosis, less rheumatoid arthritis, and – due to the effective inhibition of ovulation – less ectopic pregnancies and abortions. Treatment with OCs may also prevent bone loss in women with oligo- or amenorrhea.

Although in pill starters, inter-menstrual bleeding is frequently observed during the first to third treatment cycles, use of OCs leads to regular cycles, a reduction of menstrual blood loss and an amelioration of dysmenorrhea. Therefore, OCs may be used for treatment of various bleeding disorders (Mishell 1982).

Therapeutic use of OCs is indicated in women with irregular bleeding, menorrhagia and anemia, dysmenorrhea, and mittelschmerz. If use of combination preparations remains unsuccessful in women with intermenstrual bleeding or irregular cycles, treatment with a sequential formulation will often be effective. It is also possible to postpone withdrawal bleeding if the time of expected menses is inconvenient. By omitting the hormone-free interval of 7 days, i.e., by the uninterrupted intake of the pill for some days or weeks subsequently to the 21-day pill cycle, withdrawal bleeding is prevented. If intake is stopped, bleeding takes places within 2–4 days. By means of this procedure, the day of bleeding may be timed, although during prolonged intake, breakthrough bleeding or spotting may occur in some women.

OCs effectively reduce the serum levels of testosterone and, consequently, those of free testosterone. Therefore, some androgen-dependent symptoms, such as seborrhea, acne, hirsutism or alopecia, may be improved (Lemay et al. 1990). The therapeutic effect may be enhanced using estrogen-dominant formulations which increase the levels of SHBG, resulting in a more pronounced suppression of free testosterone levels. In more severe cases of acne and hirsutism, the use of OCs containing progestogens with anti-androgenic properties is indicated, particularly formulations with CPA. In cases with an insufficient therapeutic effect, an elevation of the CPA dose may lead to an improvement of symptoms (Moltz et al. 1980).

In women with functional ovarian cysts, treatment with OCs containing a potent progestogen component may improve complaints and prevent a relapse. Mastopathia of stage I or II may also be treated with combination OCs containing low-dose EE and a potent progestogen. Intake of this type of OC may also cause an improvement of symptoms of endometriosis.

IV. Risks and Side Effects of Oral Contraceptives

Many complaints, disorders and diseases have been ascribed to the use of OCs. Most of the epidemiological data on adverse effects of OCs have been gained from retrospective studies and refer to high-dose formulations. Nevertheless, severe diseases may also be caused by low-dose preparations. They occur, however, mostly in predisposed women; the events are rare, and a large proportion of them might be prevented by a careful examination, anamnesis and family history. Most of the disorders associated with pill use are reversed after discontinuation of OCs, and most of the subjective complaints which are known to occur during the first weeks of treatment do not differ from the effect of taking placebos.

1. Minor Complaints During Intake of Oral Contraceptives

Inter-menstrual bleeding and spotting, the incidence of which is high during the first cycle of intake and declines thereafter, may lead to a premature cessation of treatment. This type of bleeding is frequently the consequence of tablet omission and may indicate a loss of contraceptive efficacy, but is generally not a sign of disease. In most cases, inter-menstrual bleeding disappears after the third pill cycle; if not, change to a sequential formulation may lead to regular cycles, while switching to high-dose combination preparations will rarely be effective. If inter-menstrual or irregular bleeding persists, the cause must be clarified.

Amenorrhea during use of OCs ("silent menstruation") may be a consequence of high progestogenic and low estrogenic effectiveness, which results in a suppression of endometrial proliferation. It might, however, also be the result of an undesired pregnancy and has to be investigated. If amenorrhea occurs repeatedly, change to another formulation should be considered.

During the first cycle of treatment with OCs, particularly with high-dose formulations, nausea, vomiting, intestinal disorders or vertigo may occur. In most cases, the complaints disappear during further intake, but irrespective of improvement, high-dose preparations should be replaced by low-dose pills. Most subjective complaints, such as loss of libido, headaches, abdominal aches, backaches etc., are also observed during an ovulatory cycle. A placebo-controlled, blind study revealed that the incidence of such symptoms is obviously not due to an effect of the contraceptive steroids (AZNAR–RAMOS et al. 1969). In this study, only one third of the women were without side effects during intake of the placebo.

2. Fertility, Pregnancy and Lactation

In general, discontinuation of oral contraception is rapidly followed by ovulatory cycles. In nulliparous women aged more than 30 years, fertility may be slightly impaired during the first 2 years. Thereafter, no difference exists between women who had been treated with OCs and those who had used another contraceptive method. In cases of the so-called post-pill amenorrhea, i.e., long-term anovulation after cessation of OC use, a causal relationship is questionable. The rate of 1–3% in ex-users is similar to that of spontaneous secondary amenorrhea (VESSEY et al. 1978). In most of these cases, there had been irregular cycles before starting treatment with OCs. This also holds true for treatment of adolescents with OCs. There is no influence on the incidence of abortion in pregnancies after discontinuation of OC and no influence on the risk of malformations, pregnancy outcome or sex ratio of fetuses.

In a small proportion of women taking OCs, withdrawal bleeding is lacking. The uncertainty regarding pregnancy or not may lead to a continuation of pill intake early in pregnancy. As organogenesis takes place between the third and eighth weeks of fetal development (5–10 weeks since last menstruation), the question arises whether or not the use of an OC increases the

risk of congenital malformations. A *meta*-analysis revealed that intake of OCs during pregnancy does not increase the risk of malformations, the general rate of which is 2–3% (Bracken 1990).

In postpartum women, OCs may impair lactation and reduce milk volume. Moreover, the uptake by the infant of contraceptive steroids with the milk is not negligible, although no adverse effects have been observed. As the contraceptive effect of breast feeding is not reliable in all women, the use of the mini-pill is recommended.

3. Immune System

The results of some studies indicated that OCs may suppress the cellular and partly the humoral immune system, resulting in a reduction of autoimmune diseases. Treatment with an OC appears to decrease the incidence of thyroid disease and rheumatoid arthritis, particularly chronic polyarthritis. On the other hand, some data indicate that viral infections may occur more frequently during intake of OCs (Taubert and Kuhl 1995).

4. Genital Tract Infections

It is known that pelvic inflammatory disease is associated with a high risk of tubal infertility. Therefore, the protection from upper genital tract infection is an important beneficial effect of OCs. After at least 12 months of intake, the risk is reduced by 50% and, if a pelvic infection occurs, the severity of a salpingitis is decreased (Rubin et al. 1982). However, OC use increases the risk of chlamydia infection and cervicitis (Roy 1991). The latter correlates with the duration of treatment and the potency of the progestogen component.

There is no association between OC use and sexually transmitted viral disease. As OCs do not protect from human immunodeficiency virus (HIV), human papilloma virus (HPV), hepatitis B (HBV) or herpes simplex virus (HSV), the additional use of barrier methods (e.g., condom) is recommended if the risk of an infection is increased.

5. Respiratory Tract and Gingiva

OCs do not impair pulmonary function or diseases except for infections that might occur more frequently during treatment. In patients with chronic diseases, it should be kept in mind that certain drugs may interfere with the pharmacokinetics of contraceptive steroids and impair the efficacy of the OC. The EE component of OCs may stimulate proliferation of nasal and gingival mucosa (Taubert and Kuhl 1995).

The female voice is very susceptible to the influence of androgens. Therefore, treatment with OCs containing progestogens with androgenic properties may cause lowering of vocal pitch (Lembke and Freund 1990). On the other hand, estrogen-dominant OCs may stimulate edema and hyperplasia of vocal fold.

6. Eyes and Ears

There are reports of impaired vision and development of amaurosis with OC use, caused by occlusion of retinal veins or arteries. Moreover, lens opacities and ocular symptoms such as keratoconjunctivitis sicca have been observed. This may lead to contact lens wear problems. The alteration of tear composition induced by OCs may cause the formation of deposits on the contact lenses (TAUBERT and KUHL 1995).

OCs have no significant influence on hearing or on the incidence and course of otosclerosis. There are, however, some reports of sudden deafness due to an impairment of microcirculation.

7. Skin

The EE component may influence the pigment system of melanocytes. Therefore, in synergism with ultra violet (UV) light, OCs may cause changes in pigmentation. The most frequent disorder is chloasma which occurs in 20% of the women using OCs. After discontinuation, the changes are to a certain extent reversible.

The EE component may modify immunological and autoimmunological mechanisms and promote the development of erythema multiforme or nodosum and rosacea. Allergic reactions may also be induced by coloring matter contained in the tablets. The enhancement of susceptibility of the skin to exogenous agents by OCs may facilitate the development of eczema, dermatitis or urticaria. OCs may cause the manifestation or aggravation of porphyria, on the one hand, while, on the other, preventing the onset of acute intermittent porphyria during the luteal phase (TAUBERT and KUHL 1995).

8. Gastrointestinal Tract Disease

In general, there is no association between OC use and gastritis. Treatment with an OC increases, however, the risk of Crohn's disease and colitis ulcerosa (GODET et al. 1995). On the other hand, gastrointestinal bleeding may be reduced or stopped during intake of OCs.

9. Urinary Tract

OCs increase creatinine clearance and sodium and potassium excretion. There are a few casuistics of hemolytic–uremic syndrome during OC use which were due to intimal alterations and thromboses of renal arterioles or to glomerular necroses (TAUBERT and KUHL 1995). Obviously, low dose OCs do not increase infections of urinary tract. There is no information on the effect of dialysis on pharmacokinetics and efficacy of contraceptive steroids. In any case, the pill should be ingested after dialysis, and if hypertension develops, the pill has to be discontinued.

10. Endocrine Effects

In contrast to high-dose OCs, the low-dose formulations do not or only slightly increase the serum level of prolactin. In most women with an elevated prolactin concentration, the rise occurs sporadically and transitorily. In women with hyperprolactinemia or amenorrhea/galactorrhea, the use of OCs may cause a 30% rise in prolactin levels during the first cycle which remains at this range throughout further treatment.

The EE component of OCs may increase CBG levels, resulting in a rise in the serum concentrations of total cortisol. There is, however, a slight increase in free cortisol. The adrenal response to ACTH is not affected. The EE-induced rise in TBG causes an increase in T3 and T4. Thyroid function is, however, not influenced as reflected by unchanged levels of FT3, FT4 and TSH.

11. Neurological Diseases

Sex steroids may effectively influence the functional and morphological organization of the central nervous system and modulate psyche, mood and well-being. In general, estrogens may enhance neuronal activity, while progestogens may act in an antagonistic way. Reports on libido changes could not be confirmed by placebo-controlled double-blind studies. Treatment with OCs may exert a beneficial effect on the symptoms of pre-menstrual syndrome, but the success does not exceed that of a placebo.

Migraine headaches may occur during intake of OCs or during the hormone-free interval. As severe migraine or visual symptoms may be a prodrome of stroke, occurrence for the first time or an unusual worsening of the symptoms is an indication for immediate cessation of intake; although one third of patients suffering from migraine, report on an improvement during use of OCs (Mattson and Rebar 1993).

Estrogens may enhance the excitability and seizure frequency while progesterone has a sedative effect. Use of depot-MPA in addition to anti-convulsants may reduce the rate of seizures by 30%, while treatment with OCs does not influence the course of the disease. As anti-epileptics may exert a teratogenic effect, a reliable contraception is necessary. Most anti-convulsants may cause an enzyme induction and enhancement of hepatic inactivation of contraceptive steroids. Continuous use of OCs, without the hormone-free interval, or of depot-MPA may provide an increase in efficacy and prevent undesired pregnancies.

No adverse effects of OCs have been recorded with respect to multiple sclerosis or myasthenia gravis (Villard-Mackintosh and Vessey 1993). There are casuistics of other neurological diseases that developed during treatment with OCs and mostly improved or reversed after discontinuation. Some neurological diseases that may be associated with a deficiency of folic acid or vitamin B may be improved by a corresponding replacement.

12. Psychiatric Diseases

OCs have no significant influence on depression, psychosis, neurosis or phobia or other psychical diseases. Improvement, but also deterioration have been observed in some cases of menses-associated psychoses (TAUBERT and KUHL 1995). There are no data on the effect of OCs in patients with schizophrenia.

13. Physical Condition and Sports

About 10–20% of women observe an increase in body-weight during the first treatment cycles. As in double-blind studies the same effect was recorded during intake of placebos, this is probably a psychological phenomenon. In general, estrogens do not increase water retention in young women, and the weak anabolic effect of nortestosterone derivatives is without clinical relevance at the doses used in OCs. Using a high-dose OC containing 50 μg EE and 0.5 mg NG, no change in nitrogen or electrolyte balance and fat body mass could be observed (KUDZMA et al. 1972). Despite this, individual predisposed women may, however, experience an increased water retention and, consequently, a rapid weight gain. Most cases of an increase in body weight appear to be caused by an elevated caloric intake.

Low dose OCs do not decrease bone mineral content even in women with a profound suppression of ovarian estrogen synthesis, as a daily dose of 20 μg EE is sufficient for the prevention of loss of bone mass. In many high-performance athletes, irregular cycles or amenorrhea may develop resulting in an estrogen deficiency and an increased risk of stress fractures. Treatment with OCs may prevent bone loss and stress fractures.

14. Venous Complaints

In veins, EE exert a dilatory effect and increase capillary permeability, while progestogens may enhance capacitance and distensibility (FAWER et al. 1978). An increase in interstitial fluid volume in predisposed women may lead to the development of edema, "heavy legs", leg pain and cramps. The complaints depend on the EE dose and the progestogenic potency (VIN et al. 1992). In the case of severe pain and swelling in only one leg, a physician must be consulted for exclusion of a venous thrombosis.

15. Venous Thromboembolic Diseases

Treatment with OCs increase the relative risk of venous thromboembolic disease 3- to 4-fold. The incidence of deep vein thromboses and pulmonary emboli is highest during the first year of treatment, indicating a crucial role of thrombophilia, and is reversed within 4–6 weeks after cessation of OC intake. Nevertheless, the absolute risk is very low, as the annual incidence is about 4 of every 10,000 OC users. The mortality from venous thromboses and pulmonary emboli is estimated at about 5 in 1 million OC users. The most important risk factors are genetic coagulation disorders, such as resistance to

activated protein C (APC-resistance), antithrombin III-, protein C- and protein S-deficiency, anti-phospholipid-antibodies, dysfibrinogenemia, hyperhomocysteinemia, disorders of fibrinolysis and obesity. Routine screening is not recommended because of the unfavorable cost-effectiveness, but in women with a positive personal or family history, a selective thrombophilia screening may help to estimate the individual risk associated with OC use. As major surgery is also a risk factor, OC use should be stopped 4–6 weeks before an elective surgery carrying an increased risk of post-operative thrombosis.

Although epidemiological data are inconsistent due to the influence of many bias, it can be assumed that the risk increases with the EE dose of OC (Gerstman et al. 1991; Koster et al. 1995). Recent studies revealed that the use of formulations containing DG or GSD is associated with a slightly higher risk than with OCs containing LNG or NET (World Health Organization 1995; Jick et al. 1995; Bloemenkamp et al. 1995), even though the findings have been called in question. The difference was, however, most striking in first-time users, indicating that the results are not biased by a "healthy-user effect". The mechanism of action is not clarified, but it cannot be excluded that formulations containing DG and GSD may impair the anti-coagulatory system more than the other OCs (Rosing et al. 1997).

16. Stroke

Stroke is a rare event in young women. Use of OCs increases the risk of ischemic stroke 3-fold, whereby it is less in younger, normotensive and non-smoking women (World Health Organization 1996a). The relative risk is 1.5 with low-dose OCs and 5.3 with high-dose OCs, but is reversed after discontinuation of treatment. Hypertension is a strong risk factor (World Health Organization 1996a). The relative risk of hemorrhagic stroke is not increased in young women, but is doubled in women above the age of 35 years (World Health Organization 1996b). In women with a history of hypertension, treatment with an OC leads to a more than 10-fold rise in risk, while in smokers it is increased 3-fold. It is important to know that an unusual onset of visual symptoms or severe headaches may precede a stroke and is an indication to discontinue use of the pill immediately.

17. Hypertension

Treatment of women with low-dose OCs may cause a slight elevation in systolic (by 5 mmHg) and diastolic (by 2–3 mmHg) blood pressure, which is mostly reversed within 3 months after discontinuation (Godsland et al. 1995). The risk of hypertension is, however, doubled to an incidence of between 2% and 4%. The development of a high blood pressure may occur rapidly or slowly and correlates with the duration of OC treatment and age. Further risk factors are smoking, obesity, diabetes mellitus and hyperlipidemia. If blood pressure is normalized by anti-hypertensive therapy, use of OCs is possible under careful supervision. If, in this case, blood pressure rises once more, OC use has

to be stopped immediately. It has been suggested that EE is the main factor in the development of hypertension, although the progestogen component may enhance this effect. As there is no difference between hypertensive and normotensive women in the alterations of the RAA system induced by OCs, a local mechanism at the arterial wall has been proposed.

18. Myocardial Infarction

In young women, myocardial infarction is a very rare event, and the annual mortality rate is 2 in 100,000 women. In total, the relative risk is increased 5-fold by OC use; however, young women who do not smoke and have no other risk factors are not affected (WORLD HEALTH ORGANIZATION 1997). In heavy smokers, the relative risk increases 20-fold during OC treatment. Further risk factors are age, hypertension, diabetes mellitus, obesity, hyperlipoproteinemia, hyperfibrinogenemia and elevated blood viscosity (CROFT and HANNAFORD 1989). Epidemiological data indicate an involvement of the progestogen component in the development of arterial diseases (KAY 1982; WINGRAVE 1982; MEADE 1988). There is, however, no evidence that the risk is higher when OCs containing LNG or NET are used. Although formulations with an overweigh of the androgenic effect of the progestogen may cause deleterious alterations in lipid metabolism, no accelerated development of atherosclerosis has been observed. This might be due to the anti-oxidative effect of EE which may act as a free radical scavenger and prevent LDL oxidation. It is known that estrogens exert a dilatory, and progestogens a constrictor effect on the arterial wall. At sites of arterial lesions, e.g., in smokers, the progestogen might enhance vasospasms and trigger an arterial thrombosis.

19. Raynaud's Syndrome

Treatment with OCs appears to increase to risk of development of Raynaud's syndrome. Although there is no evidence of a deterioration of the symptoms of Raynaud's syndrome with OC use, the pill should not be used in patients with disturbed peripheral circulation. In cases of occlusion of retinal vessels or changes in renal microcirculation, an improvement may be observed after discontinuation of OCs.

20. Diabetes Mellitus

During intake of OCs, a slight insulin resistance and impairment of glucose tolerance is observed that is compensated by a small increase in insulin levels and reversed after discontinuation (GODSLAND and CROOK 1994; GODSLAND et al. 1990). The mechanism is not clarified, but it is suggested that EE reduces insulin clearance, while the progestogen component impairs peripheral glucose consumption (TAUBERT and KUHL 1995). There are no epidemiological data indicating that OCs may cause diabetes mellitus, neither in women with normal glucose tolerance nor in patients with pathological values. The

proportion of women with an impaired glucose tolerance is, however, doubled by treatment with OCs. In contrast, the progression to diabetes mellitus is independent of OC use (Duffy and Ray 1984).

Patients with manifest type-I diabetes mellitus (IDDM) who need a reliable contraception may use OCs under careful supervision, provided that no macro- or microangiopathies exist. It is also important to pay attention to additional risk factors. Use of OCs in young women with insulin-dependent diabetes mellitus probably does not additionally impair endothelial function (Petersen et al. 1994; Garg et al. 1994).

21. Liver

Except for rare liver tumors, the relative risk of which is elevated during long-term OC use, the incidence of serious liver diseases among current or former pill users is not significantly influenced. There was, however, a modestly increased risk of mild liver disease, which declined after 4 years of use and after discontinuation (Hannaford et al. 1997).

It is known that synthetic sex steroids containing an ethinyl group, particularly EE, may impair hepatic functions and cause morphological alterations of the liver. In 1% of women, a rise in serum liver-enzyme parameters is observed during the first cycles of treatment with low-dose OCs, which mostly normalizes thereafter. In patients with severe chronic liver disease, all synthetic steroids are contraindicated.

EE and nortestosterone derivatives may impair the excretory function of the liver and change the composition of bile. In women with a reduced excretory capacity, an intra-hepatic cholestasis may develop during the first six cycles of treatment with OCs, leading to pruritus and jaundice (Rannevik et al. 1972). In most cases, it is reversed within 2 months after discontinuation.

In predisposed women, treatment with OCs may lead to an excessive increase in porphyrin precursors, resulting in the manifestation of porphyria (Doss 1984). In most cases, the symptoms are rapidly reversible after stopping pill intake. In some patients with acute intermittent porphyria, who frequently suffer from an outburst during the luteal phase, treatment with OCs may even stabilize the latent sub-clinical phase of the disease.

OCs do not influence the development or course of hepatitis (Schweitzer et al. 1975). In women with a history of hepatitis, the liver function parameters may increase markedly during the first cycles of OC treatment (Shaaban et al. 1982). If the elevated values still persist after 6 months, the pill should be discontinued.

The prevalence of gall bladder disease in women is about 4% and is 4- to 5-fold higher in patients with a positive family history, indicating the role of predisposition. OCs may cause a premature manifestation of cholelithiasis or cholecystitis, but the total risk of gall bladder diseases is not influenced by the pill (Vessey and Painter 1994; Grodstein et al. 1994).

In women with a latent hyperlipoproteinemia type IV or V, EE may cause an excessive rise in TGs. Therefore, during treatment with estrogen-dominant OCs, predisposed women may develop a pancreatitis within three cycles that is reversible after cessation of intake.

22. Liver Tumors

Benign liver tumors are an extremely rare event, the relative risk of which is, however, increased by OC use (ROOKS et al. 1979). The effect depends on the duration of treatment and the dose and potency of EE and the progestogen. Moreover, a genetic predisposition appears to play a role. Even though most liver adenomas regress after discontinuation of the pill, their importance lies in the risk of rupture and intraperitoneal hemorrhage, which is higher for liver cell adenomas than for focal nodular hyperplasias. Regular palpation of the liver may help to recognize liver tumors.

The development of hepatocellular carcinomas, which is also a very rare event, is mostly associated with liver cirrhosis due to hepatitis B infection or alcohol abuse. Long-term treatment with an OC appears to increase the relative risk (NEUBERGER et al. 1986; ROSENBERG 1991).

23. Breast

In 2–5% of women taking OCs, an enhanced fluid retention may lead to an increase in breast volume, which may cause mastodynia. Treatment with combination formulations with low EE and a potent progestogen or with depot-progestogens may improve the condition. During use of OCs, the risk of benign breast disease is reduced. This beneficial effect correlates with the duration of treatment and potency of the progestogen component (ROYAL COLLEGE OF GENERAL PRACTITIONERS 1977). Therefore, in women with mastopathia grade I or II, the use of formulations with a potent progestogen is recommended.

24. Breast Cancer

Nearly 30% of all cancers in women concerns breast cancer, and about 10% of the women will develop breast cancer during their lifetime. In young women, the disease is rare, but increases markedly with age. Numerous case-control and prospective studies have been carried out regarding the effect of OCs on breast-cancer risk. Due to the long latency of the disease and the relative small case numbers in younger women, the results were inconsistent, particularly with respect to sub-groups.

A re-analysis of the individual data of more than 50,000 women with breast cancer and 100,000 controls from 54 studies was published in 1996 (COLLABORATIVE GROUP ON HORMONAL FACTORS IN BREAST CANCER 1996). The results clearly show that during current use of OCs, there is a small increase in the relative risk of a breast cancer diagnosis of 24%, which is reversed

during the first 10 years after discontinuation. The additional cases diagnosed in women who had used OC are less advanced and have a better prognosis than those diagnosed in women who had never used OCs. The extremely small risk associated with OC use is exemplified by the small number of additional breast cancers. Among 10,000 women, between the age of 25 years and 29 years, who take OCs for 5 years, there will be seven additional localized breast cancers diagnosed before age 50, while there will be a deficit of four breast cancers spread beyond the breast. The cumulative number of breast cancers additionally diagnosed in 10,000 women in the period between starting OC use and 10 years after stopping are 0.5 in women aged 16–19 years, 1.5 in those aged 20–24 years, 4.7 in those aged 25–29 years and 11.1 in those aged 30–34 years. The relative risk associated with OCs was not influenced by dose or composition of the pill, duration of treatment, parity, time of first childbirth, family history, body mass index or alcohol. The effect appears to be due to an increase in the proportion of proliferative epithelial cells (Williams et al. 1991) and a stimulation of growth of that proportion of the tumor which still is controlled by estrogens.

25. Uterine Tumors

Treatment with OCs containing a low EE dose and a potent progestogen component may reduce rather than increase the incidence of uterine myoma. As growth of uterine myoma is estrogen-dependent, depot-progestogens should be preferred. Progestogen-dominant OCs may also improve symptoms of endometriosis, but cannot cause atrophy of endometriotic tissue.

Long-term unopposed influence of endogenous estrogens as observed in persisting anovulatory cycles or polycystic-ovary syndrome, may cause endometrial hyperplasia and cancer. The regular influence of the progestogen contained in combined OCs protects from the development of endometrial hyperplasia and reduces the relative risk of endometrial cancer by 50% (Schlesselman 1991; Stanford et al. 1993). The beneficial effect is greatest after 3 years of intake and persists after discontinuation of the pill for many years. It can be assumed that the use of sequential formulations with 15 days of progestogenic influence per cycle also protects from endometrial carcinoma.

As OCs do not stimulate growth of trophoblastic cells, the incidence of hydatidiform mole or chorionic carcinoma is not increased.

26. Cervical Neoplasia

During use of OCs, endocervical glandular hypersecretion and proliferation of endocervical glands may be observed, which are suggested to be induced primarily by the progestogen component. Similarly, the occurrence of metaplasia and dysplasia of the uterine cervix have been ascribed to the action of progestogens.

Epidemiological findings indicate that OCs increase the risk of carcinoma-in-situ and invasive carcinoma of the uterine cervix, time-dependently,

particularly in adolescents (WORLD HEALTH ORGANIZATION 1985; BRINTON et al. 1986). The results are, however, not definitive, as the role of other important risk factors, such as smoking and sexual behavior, have not been clarified. It is known that infection with human papilloma virus is involved in the development of cervical neoplasia (BOSCH et al. 1992), and contraceptive barrier methods may reduce the risk. Regular examination and *Pap* smear in women who use OCs may also contribute to preventing invasive cervical cancer (PARAZZINI et al. 1997).

27. Ovarian Tumors

The incidence of functional ovarian cysts is reduced by the use of combined OCs. Moreover, existing functional ovarian cysts may regress during treatment with OCs. Ovulation inhibitors also reduce the relative risk of epithelial ovarian cancer by 40%. This important protective effect correlates with the duration of treatment and persists for at least 10 years after discontinuation of the pill (WHITTEMORE et al. 1992).

28. Other Cancers

Similar to cervical cancer, the risk of vulvar cancer correlates with the number of sexual partners and is decreased by the use of contraceptive barrier methods. No influence on the relative risk of vulvar cancer with OC use could, however, be observed.

OCs do not influence the incidence of prolactinoma and, in patients with microprolactinoma, OCs may be used after normalization of prolactin levels by treatment with dopamine agonists.

Although estrogens may influence melanocytes in synergism with UV light and may cause hyperpigmentation, there is no evidence that OCs may influence the incidence of malignant melanoma (PALMER et al. 1992). Therefore, a history of melanoma is no contraindication for hormonal contraception.

Even though estrogen and progesterone receptors have been demonstrated to be present in nearly every tissue, no other malignant tumors have been shown to be promoted by the use of OCs.

References

Aznar-Ramos R, Giner-Velasquez J, Lara-Ricalde R, Martinez-Manautou J (1969) Incidence of side-effects with contraceptive placebo. Am J Obstet Gynecol 105: 1144–1149

Back DJ, Barkfeldt JO, Breckenridge AM, Odlind V, Orme M, Park BK, Purba H, Tjia J, Victor A (1982) The enzyme inducing effect of rifampicin in the rhesus monkey and its lack of interaction with oral contraceptive steroids. Contraception 25:307–316

Back DJ, Grimmer SFM, Orme ML'E, Proudlove C, Mann RD, Breckenridge AM (1988) Evaluation of committee on safety of medicines yellow card reports on oral

contraceptive-drug interactions with anticonvulsants and antibiotics. Br J Clin Pharmacol 25:527–532
Back DJ, Orme MLE (1990) Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet 18:472–484
Ball MJ, Ashwell E, Jackson M, Gillmer MDG (1990) Comparison of two triphasic contraceptives with different progestogens: effects on metabolism and coagulation proteins. Contraception 41:363–376
Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, Büller HR, Vandenbroucke JP (1995) Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. Lancet 346:1593–1596
Bosch FX, Munoz N, de Sanjose S, Izarzugaza I, Gili M, Viladiu P et al. (1992) Risk factors for cervical cancer in Colombia and Spain. Int J Cancer 52:750–758
Bracken MB (1990) Oral contraception and congenital malformations in offspring: A review and meta-analysis of the prospective studies. Obstet Gynecol 76:552–557
Brinton LA, Huggins GR, Lehman HF, Mallin K, Savitz DA, Trapido E, Rosenthal J, Hoover R (1986) Long-term use of oral contraceptives and risk of invasive cervical cancer. Int J Cancer 38:339–344
Brosens IA, Pijnenborg R (1976) Comparative study of the estrogenic effect of ethinylestradiol and mestranol on the endometrium. Contraception 14:679–685
Cohen H, Mackie IJ, Walshe K, Gillmer MDG, Machin SJ (1988) A comparison of the effects of two triphasic oral contraceptives on haemostasis. Br J Haematol 69:259–263
Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet 347:1713–1727
Croft P, Hannaford PC (1989) Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. Br Med J 298:165–168
Crook D, Godsland IF, Wynn V (1988) Oral contraceptives and coronary heart disease: modulation of glucose tolerance and plasma lipid risk factors by progestins. Am J Obstet Gynecol 158:1612–1620
Daly L, Bonnar J (1990) Comparative studies of 30μg ethinylestradiol combined with gestodene and desogestrel on blood coagulation, fibrinolysis, and platelets. Am J Obstet Gynecol 163:430–437
Derkx FHM, Stünkel C, Schalekamp MPA, Visser W, Huisveld IH, Schalekamp MADH (1986) Immunoreactive renin, prorenin, and enzymatically active renin in plasma during pregnancy and in women taking oral contraceptives. J Clin Endocrinol Metab 63:1008–1015
Doss M (1984) Porphyrie und hormonale Kontrazeptiva. Dtsch Med Wschr 109:1701–1702
Duffy TJ, Ray R (1984) Oral contraceptive use: prospective follow-up of women with suspected glucose intolerance. Contraception 40:197–208
Fawer R, Dettling A, Weihs D, Welti H, Schelling JL (1978) Effect of the menstrual cycle, oral contraception and pregnancy on forearm blood flow, venous distensibility and clotting factors. Eur J Clin Pharmacol 13:251–257
Fern M, Rose DP, Fern EB (1978) Effect of oral contraceptives on plasma androgenic steroids and their precursors. Obstet Gynecol 51:541–544
Fisch IR, Frank J (1977) Oral contraceptives and blood pressure. J Am Med Ass 237:2499–2503
Garg SK, Chase HP, Marshall G, Hoops SL, Holmes DL, Jackson WE (1994) Oral contraceptives and renal and retinal complications in young women with insulin-dependent diabetes mellitus. J Am Med Ass 271:1099–1102

Gerstman BB, Piper JM, Tmita DK, Ferguson WJ (1991) Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. Am J Epidemiol 133:32–36
Godet PG, May GR, Sutherland LR (1995) Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. Gut 37:668–673
Godsland IF, Crook D (1994) Update on the metabolic effects of steroidal contraceptives and their relationship to cardiovascular disease risk. Am J Obstet Gynecol 170:1528–1536
Godsland IF, Crook D, Davenport M, Wynn V (1995) Relationships between blood pressure, oral contraceptive use and metabolic risk markers for cardiovascular disease. Contraception 52:143–149
Godsland IF, Crook D, Wynn V (1990) Low-dose oral contraceptives and carbohydrate metabolism. Am J Obstet Gynecol 163:348–353
Grodstein F, Colditz GA, Hunter DJ, Manson JE, Willett WC, Stampfer MJ (1994) A prospective study of symptomatic gallstones in women: relation with oral contraceptives and other risk factors. Obstet Gynecol 84:207–214
Hannaford PC, Kay CR, Vessey MP, Painter R, Mant J (1997) Combined oral contraceptives and liver disease. Contraception 55:145–151
Haspels AA (1994) Emergency contraception: a review. Contraception 50:101–108
Jick H, Jick SS, Gurewich V, Myeres MW, Vasilakis C (1995) Risk of idiopathic cardiovascular death and non-fatal venous thromboembolism in women using oral contraceptives with differing progestagen components. Lancet 346:1589–1593
Jung-Hoffmann C, Kuhl H (1987) Divergent effects of two low-dose oral contraceptives on sex hormone-binding globulin and free testosterone. Am J Obstet Gynecol 156:199–203
Jung-Hoffmann C, Kuhl H (1990) Intra- and interindividual variations in contraceptive steroid levels during 12 treatment cycles: no relation to irregular bleedings. Contraception 42:423–438
Jung-Hoffmann C, Heidt F, Kuhl H (1988) Effect of two oral contraceptives containing 30μg ethinylestradiol and 75μg gestodene or 150μg desogestrel upon various hormonal parameters. Contraception 38:593–603
Kay CR (1982) Progestogens and arterial disease – evidence from the Royal College of General Practitioners' study. Am J Obstet Gynecol 142:762–765
Knopp RH, LaRosa JC, Burkman RT (1993) Contraception and dyslipidemia. Am J Obstet Gynecol 168:1994–2005
Koster T, Small RA, Rosendaal FR, Helmerhorst FM (1995) Oral contraceptives and venous thromboembolism: a quantitative discussion of the uncertainties. J Int Med 238:31–37
Krauss RM, Burkman RT (1992) The metabolic impact of oral contraceptives. Am J Obstet Gynecol 167:1177–1184
Kudzma DJ, Bradley EM, Goldzieher JW (1972) A metabolic balance study of the effects of an oral steroid contraceptive on weight and body composition. Contraception 6:31–37
Kuhl H (1990a) Pharmacokinetics of estrogens and progestogens. Maturitas 12:171–197
Kuhl H (1994a) Wie Darmerkrankungen, Ernährung, Rauchen und Alkohol die Wirkung von oralen Kontrazeptiva beeinflussen. Geburtsh Frauenheilk 54:M1–M10
Kuhl H (1994b) Wie sich orale Kontrazeptiva und Medikamente in ihrer Wirkung beeinflussen. Geburtsh Frauenheilk 54:M23–M30
Kuhl H (1996a) Comparative pharmacology of newer progestogens. Drugs 51:188–215
Kuhl H (1996b) Effects of progestogens on haemostasis. Maturitas 24:1–19
Kuhl H, Gahn G, Romberg C, Althoff PH, Taubert HD (1985a) A randomized crossover comparison of two low-dose oral contraceptives upon hormonal and metabolic parameters: II.Effects on thyroid function, gastrin, STH, and glucose tolerance. Contraception 32:97–107

Kuhl H, Gahn G, Romberg C, März W, Taubert HD (1985b) A randomized cross-over comparison of two low-dose oral contraceptives upon hormonal and metabolic parameters: I. Effects upon sexual hormone levels. Contraception 31:583–593
Kuhl H, März W, Jung-Hoffmann C, Heidt F, Gross W (1990b) Time-dependent alterations and lipid metabolism during treatment with low-dose oral contraceptives. Am J Obstet Gynecol 163:363–369
Kuhl H, März W, Jung-Hoffmann C, Weber J, Siekmeier R, Gross W (1993) Effect on lipid metabolism of a biphasic desogestrel-containing oral contraceptive: divergent changes in apolipoprotein B and E and transitory decrease in Lp (a) levels. Contraception 47:69–83
Lemay A, Dodin Dewailly S, Grenier R, Huard J (1990) Attenuation of mild hyperandrogenic activity in postpubertal acne by a triphasic oral contraceptive containing low doses of ethynyl estradiol and d,l-norgestrel. J Clin Endocrinol Metab 71:8–14
Lembke S, Freund H (1990) Einfluß hormonaler Kontrazeptiva auf die Stimme. Z Ärztl Fortb 84:47–49
Mandel FP, Geola FL, Lu JKH, Eggena P, Sambhi MP, Hershman JM, Judd HL (1982) Biologic effects of various doses of ethinyl estradiol in postmenopausal women. Obstet Gynecol 59:673–679
Mashchak CA, Lobo RA, Dozono-Takano R, Eggena P, Nakamura RM, Brenner PF, Mishell DR (1982) Comparison of pharmacodynamic properties of various estrogen formulations. Am J Obstet Gynecol 144:511–518
Mattson RH, Rebar RW (1993) Contraceptive methods for women with neurologic disorders. Am J Obstet Gynecol 168:2027–2032
McCann MF, Potter LS (1994) Progestin-only oral contraception: a comprehensive review. Contraception 50(Suppl.1):S1–S198
Meade TW ((1988) Risks and mechanisms of cardiovascular events in users of oral contraceptives. Am J Obstet Gynecol 158:1646–1652
Mishell DR (1982) Noncontraceptive health benefits of oral steroidal contraceptives. Am J Obstet Gynecol 142:809–816
Moltz L, Schwartz U, Hammerstein J (1980) Die klinische Anwendung von Antiandrogenen bei der Frau. Gynäkologe 13:1–17
Neuberger J, Forman D, Doll R, Williams R (1986) Oral contraceptives and hepatocellular carcinoma. Br Med J 292:1355–1357
Olivieri O, Friso S, Manzato F, Grazioli S, Bernardi F, Lunghi B, Girelli D, Azzini M, Brocco G, Russo C, Corrocher R (1996) Resistance to activated protein C, associated with oral contraceptives use; effect of formulations, duration of assumption, and doses of oestro-progestins. Contraception 54:149–152
Palmer JR, Rosenberg L, Strom BL, Harlap S, Zauber AG, Warshauer ME, Shapiro S (1992) Oral contraceptive use and risk of cutaneous malignant melanoma. Cancer Causes Control 3:547–554
Parazzini F, LaVecchia C, Negri E, Franceschi S, Moroni S, Chatenoud L, Bolis G (1997) Case-control study of estrogen replacement therapy and risk of cervical cancer. Br Med J 315:85–88
Petersen KR, Skouby SO, Sidelmann J, Jespersen J (1994) Assessment of endothelial function during oral contraception in women with insulin-dependent diabetes mellitus. Metabolism 43:1379–1383
Petersen KR, Sidelmann J, Skouby SO, Jespersen J (1993) Effects of monophasic low-dose oral contraceptives on fibrin formation and resolution in young women. Am J Obstet Gynecol 168:32–38
Population Reports (1995) Injectables and implants – new era for injectables. Series K:1–31
Population Reports (1992) Decisions for Norplant programs. Series K:1–31
Rannevik G, Jeppson S, Kullander S (1972) Effect of oral contraceptives on the liver in women with recurrent cholestasis (hepatosis) during previous pregnancies. J Obstet Gynaecol Br Cmwlth 79:1128–1136

Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Hennekens CH, Speizer FE (1992) Oral contraceptive use and risk of type 2 (non-insulin-dependent) diabetes mellitus in a large prospective study of women. Diabetologia 35:967–972

Rooks JB, Ory HW, Ishak K, Strauss LT, Greenspan JR, Paganini-Hill A, Tyler CW (1979) Epidemiology of hepatocellular adenoma. The role of oral contraceptive use. J Am Med Ass 242:644–648

Rosenberg L (1991) The risk of liver neoplasia in relation to combined oral contraceptive use. Contraception 43:643–652

Rosing J, Tans G, Nicolaes GAF, Thomassen MCLGD, van Oerle R, van der Ploeg PMEN, Heijnen P, Hamulyak K, Hemker HC (1997) Oral contraceptives and venous thrombosis: different sensitivities to activated protein C in women using second- and third- generation oral contraceptives. Br J Haematol 97:233–238

Roy S (1991) Nonbarrier contraceptives and vaginitis and vaginosis. Am J Obstet Gynecol 165:1240–1244

Royal College of General Practitioners' Oral Contraceptive Study (1977) Effect on hypertension and benign breast disease of progestagen component in combined oral contraceptives. Lancet I:624

Rubin GL, Ory HW, Layde PM (1982) Oral contraceptives and pelvic inflammatory disease. Am J Obstet Gynecol 144:630–635

Schlesselman JJ (1991) Oral contraceptives and neoplasia of the uterine corpus. Contraception 43:557–580

Schweitzer IL, Weiner JM, McDeak CM, Thursby MW (1975) Oral contraceptives in acute viral hepatitis. J Am Med Ass 233:979–980

Shaaban MM, Hammad WA, Fathalla MF, Ghaneimah SA, El-Sharkawy MM, Salim TH, Ali MY, Liao WC, Smith SC (1982) Effects of oral contraception on liver function tests and serum proteins in women with past viral hepatitis. Contraception 26:65–74

Stanczyk FZ (1997) Pharmacokinetics of the new progestogens and influence of gestodene and desogestrel on ethinylestradiol metabolism. Contraception 55:273–282

Stanczyk FZ, Roy S (1990) Metabolism of levonorgestrel, norethindrone, and structurally related contraceptive steroids. Contraception 42:67–96

Stanford JL, Brinton LA, Berman R, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, Hoover RN (1993) Oral contraceptives and endometrial cancer: do other risk factors modify the association? Int J Cancer 54:243–248

Steingold KA, Cefalu W, Pardridge W, Judd HL, Chaudhuri G (1986) Enhanced hepatic extraction of estrogens used for replacement therapy. J Clin Endocrinol Metab 62:761–766

Szoka PR, Edgren RA (1988) Drug interactions with oral contraceptives: compilation and analysis of an adverse experience report database. Fertil Steril (Suppl) 49:31–38

Taubert HD, Kuhl H (1995) Kontrazeption mit Hormonen, 2nd edn, Thieme, Stuttgart New York

van der Vange N, Blankenstein MA, Kloosterboer HJ, Haspels AA, Thijssen JHH (1990) Effects of seven low-dose combined oral contraceptives on sex hormone binding globulin, corticosteroid binding globulin, total and free testosterone. Contraception 41:345–352

Vessey MP, Lawless M, McPherson K, Yeates D (1985) Progestogen-only oral contraceptives. Findings in a large prospective study with special reference to effectiveness. Br J Family Plann 10:117–121

Vessey MP, Painter R (1994) Oral contraceptive use and benign gallbladder disease; revisited. Contraception 50:167–173

Vessey MP, Wright NH, McPherson K, Wiggins P (1978) Fertility after stopping different methods of contraception. Br Med J I:265–267

Villard-Mackintosh L, Vessey MP (1993) Oral contraceptives and reproductive factors in multiple sclerosis incidence. Contraception 47:161–168

Vin F, Allaert FA, Levardon M (1992) Influence of estrogens and progesterone on the venous system of the lower limbs in women. Phlebology 18:888–892
Weir RJ, Davies DL, Fraser R, Morton JJ, Tree M, Wilson A (1975) Contraceptive steroids and hypertension. J Steroid Biochem 6:961–964
Whittemore AS, Harris R, Intyre J, and the Collaborative Ovarian Cancer Group (1992) Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. Am J Epidemiol 136:1184–1203
Williams G, Anderson E, Howell A, Watson R, Coyne J, Roberts SA, Potten CS (1991) Oral contraceptive (OCP) use increases proliferation and decreases estrogen receptor content of epithelial cells in the normal human breast. Int J Cancer 48:206–210
Wingrave SJ (1982) Progestogen effects and their relationship to lipoprotein changes. Acta Obstet Gynecol Scand (Suppl) 105:33–36
World Health Organisation Collaborative Study of Neoplasia and Steroid Contraceptives (1985) Invasive cervical cancer and combined oral contraceptives. Br Med J 190:961–965
World Health Organisation Task Force for Epidemiological Research on Reproductive Health (1994a) Progestogen-only contraceptives during lactation: I. Infant growth. Contraception 50:35–53
World Health Organisation Task Force for Epidemiological Research on Reproductive Health (1994b) Progestogen-only contraceptives during lactation: II. Infant development. Contraception 50:55–68
World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (1995) Effect of different progestagens in low estrogen oral contraceptives on venous thromboembolic disease. Lancet 346:1582–1588
World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid hormone Contraception (1996a) Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. Lancet 348:498–504
World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (1996b) Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study Lancet 348:505–510
World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (1997) Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study, Lancet 349:1202–1209
Wynn V (1982) Effect of duration of low-dose oral contraceptive administration on carbohydrate metabolism. Am J Obstet Gynecol 142:739–746
Yuzpe AA, Smith RP, Rademaker AW (1982) A multicentre clinical investigation employing ethinylestradiol combined with dl-norgestrel as a postcoital contraceptive agent, Fertil Steril 37:508–513