COMBINED ESTROGEN–PROGESTOGEN CONTRACEPTIVES

Combined Oral Estrogen–Progestogen Contraceptives (Group 1)

VOL.: 91

5. Summary of Data Reported and Evaluation

5.1 Exposure data

The first oral hormonal contraceptives that were were found to inhibit both ovulation and implantation were developed in the 1950s and included both estrogen and progestogen. Since that time, changes in component ingredients, doses used and the temporal sequencing of exposure to hormones have occurred with emerging technologies and in an effort to reduce adverse effects. The dominant trends in recent years have been towards the use of lower doses of estrogen, use of progestogens that are less androgenic, the multiplication of product formulations and the continuing development of novel delivery systems. In current preparations, ethinylestradiol is the most common estrogen, although a variety of other estrogens is also available. An even greater range of progestogens is used. The estrogen and progestogen components are usually given together orally in a monthly cycle, e.g. 21 days of constant or varying doses followed by 7 days without hormones. Combined hormonal contraceptives can also be administered by injection, transdermal patch and vaginal device. In addition to their regular use for contraception, other common indications for these products include emergency contraception, and the treatment of acne and menstrual disorders. Some commonly used formulations, doses, routes of administration and schedules of exposure are new and their possible long-term adverse effects have not been evaluated.

Worldwide, more than 100 million women — an estimated 10% of all women of reproductive age — currently use combined hormonal contraceptives, a large majority of which are in the form of oral preparations. Current use of these drugs is greatest in developed countries (16%) and is lower in developing countries (6%). Rates of ‘ever use’ higher than 80% have been reported for some developed countries. In developing countries, 32% of women were estimated to have ever used hormonal contraception. Overall, the use of combined hormonal contraception is increasing, but there is extreme variability between countries. In many countries, these preparations are mainly used by women of younger age and higher level of education, and who have greater access to health care.

5.2 Human carcinogenicity data

Breast cancer

More than 10 cohort studies and 60 case–control studies that included over 60 000 women with breast cancer reported on the relationship between the oral use of combined hormonal contraceptives and the risk for this disease. The totality of the evidence suggested an increase in the relative risk for breast cancer among current and recent users. This effect was noted particularly among women under 35 years of age at diagnosis who had begun using contraceptives when young (< 20 years), whereas the increased risk declined sharply with older age at diagnosis. By 10 years after cessation of use, the risk in women who had used combined hormonal contraceptives appeared to be similar to that in women who had never

used them. Important known risk factors did not appear to account for the association. The possibility that the association seen for current and recent users is due to detection bias was not ruled out, but it was considered to be unlikely that this would explain the association observed in young women.

Endometrial cancer

Four cohort studies and 21 case–control studies reported on the relationship between the oral use of combined hormonal contraceptives and the risk for endometrial cancer. The results of these studies consistently showed that the risk for endometrial cancer in women who had taken these medications is approximately halved. The reduction in risk was generally greater with longer duration of use of combined hormonal contraceptives and persisted for at least 15 years after cessation of use, although the extent of the protective effect may wane over time. Few data were available on the more recent, low-dose formulations.

Cervical cancer

Five cohort and 16 case–control studies of the oral use of combined hormonal contraceptives and invasive cervical cancer were reviewed in the previous Monograph on this topic. That Working Group could not rule out biases related to sexual behaviour, screening and other factors as possible explanations for the observed association with increasing duration of use.

Since that time, two cohort and seven case–control studies have provided new information on invasive or in-situ carcinoma and oral use of combined hormonal contraceptives; all but the three most recent studies were summarized in a meta-analysis of published data. The totality of the evidence indicated that, overall, the risk for cervical cancer increased with increasing duration of use of combined hormonal contraceptives, and was somewhat greater for in-situ than for invasive cancer. The relative risk appeared to decline after cessation of use. The results were broadly similar regardless of adjustment for the number of sexual partners, cervical screening, smoking and the use of barrier contraceptives. The association was found in studies conducted in both developed and developing countries. The possibility that the observed association is due to detection bias was not ruled out, but it was considered to be unlikely that this would explain the increase in risk. Studies in which information on human papillomavirus infection — the main cause of cervical cancer — was available suggested that the prevalence of the infection was not increased among users of combined hormonal contraceptives, and the association with cervical cancer was also observed in analyses that were restricted to human papillomavirus-positive cases and controls.

Ovarian cancer

Data from an additional three cohort and 20 case–control studies that had been updated since the last Monograph or were new showed that women who had ever used combined hormonal contraceptives orally had an overall reduced risk for ovarian cancer and that an inverse relationship was observed with duration of use. The reduced risk appeared to persist for at least 20 years after cessation of use. The effect of combined hormonal contraceptives on the reduction of risk for ovarian cancer is not confined to any particular type of oral formulation nor to any histological type of ovarian cancer, although it is less consistent for mucinous than for other types in several studies.

Cancer of the liver

Long-term oral use of combined hormonal contraceptives was associated with an increase in the risk for hepatocellular carcinoma in all nine case–control studies conducted in populations with low prevalences of hepatitis B viral infection and chronic liver disease — which are major causes of liver cancer — and in analyses in which women with such infections were excluded. Three cohort studies showed no significant association between the oral use of combined hormonal contraceptives and the incidence of or mortality from liver cancer, but the expected number of cases was very small, resulting in low statistical power. Few data were available for the more recent, low-dose formulations. In the three case–control studies conducted in populations with a high prevalence of infection with hepatitis viruses, there was no statistically significant increase in the risk for hepatocellular carcinoma associated with the oral use of combined hormonal contraceptives, but little information was available on long-term use.

Cutaneous melanoma

Four cohort and 16 case–control studies provided information on the oral use of combined hormonal contraceptives and the risk for cutaneous malignant melanoma. No consistent evidence for an association was found with respect to current use, duration of use, time since last use or age at first use. The few studies that suggested an increase in risk may reflect the possibility that women who took oral contraceptives may have had more contacts with the medical system and were thus more likely to have had pigmented lesions removed.

Colorectal cancer

Seven cohort and 13 case–control studies provided information on the oral use of combined hormonal contraceptives and the risk for colorectal cancer. Most studies did not show an increase in risk in women who had ever used contraceptives or in relation to duration of use. The results were generally similar for colon and rectal cancer when examined separately, and two case–control studies showed a significant reduction in risk.

5.3 Carcinogenicity in experimental animals

The data evaluated in this section showed a consistent carcinogenic effect of several estrogen–progestogen combinations across different animal models in several organs. There was not enough evidence of carcinogenicity for one of the newer progestogens studied, dienogest.

Estrogen–progestogen combinations

In female and male mice, the incidences of pituitary adenoma were increased by administration of mestranol plus chlormadinone acetate, mestranol plus ethynodiol diacetate, ethinylestradiol plus ethynodiol diacetate, mestranol plus norethisterone, ethinylestradiol plus norethisterone (females only) and mestranol plus norethynodrel, which also increased the incidence of pituitary adenomas in female rats.

The incidence of benign mammary tumours was increased in female and male mice by ethinylestradiol plus megestrol acetate, in female and male rats by ethinylestradiol plus ethynodiol diacetate, in female rats by mestranol plus norethisterone, mestranol plus

norethynodrel and ethinylestradiol plus norethisterone acetate, in intact and castrated male mice by ethinylestradiol plus chlormadinone acetate and in castrated male mice by mestranol plus norethynodrel. Ethinylestradiol plus norethisterone acetate did not cause tumour formation in any tissue in one study in female monkeys.

In female mice, the incidence of malignant non-epithelial uterine tumours was increased by ethinylestradiol plus ethynodiol diacetate and the incidence of vaginal or cervical tumours by norethynodrel plus mestranol. In female mice treated with 3-methylcholanthrene to induce genital tumours, ethinylestradiol plus lynestrenol, ethinylestradiol plus norgestrel and mestranol plus norethynodrel increased the incidence of uterine tumours; however, this occurred only at the highest doses of ethinylestradiol plus lynestrenol and ethinylestradiol plus norgestrel that were tested. Lower doses inhibited tumorigenesis induced by 3-methylcholanthrene alone.

In female rats, the incidence of hepatocellular carcinomas was increased by ethinylestradiol plus norethisterone acetate; the latter combination and mestranol plus norethisterone also increased the incidence of liver adenomas in male rats. Liver foci, which are putative preneoplastic lesions, were induced in female rats by mestranol plus norethynodrel. In female rats initiated for hepatocarcinogenesis with *N*-nitrosodiethylamine, mestranol plus norethynodrel increased the formation of altered hepatic foci.

In one study, subcutaneous administration of levonorgestrel with ethinylestradiol or estradiol to female rabbits induced deciduosarcomas in several organs (uterus, spleen, ovary, liver and lung).

Estrogens

The incidence of pituitary adenomas was increased by ethinylestradiol and mestranol in female and male mice and by ethinylestradiol in female rats.

The incidences of malignant mammary tumours in female and male mice and female rats were increased by ethinylestradiol and mestranol; however, mestranol did not increase the incidences of mammary tumours in female dogs in a single study.

Ethinylestradiol increased the incidence of cervical tumours in female mice.

In female and male mice, ethinylestradiol increased the incidences of hepatocellular adenomas. In female rats, ethinylestradiol and mestranol increased the numbers of altered hepatic foci. In rats, ethinylestradiol increased the incidence of adenomas in females and males and of hepatocellular carcinomas in females, whereas mestranol increased the incidence of hepatic nodules and carcinomas combined in females.

The incidence of microscopic malignant kidney tumours was increased in male hamsters exposed to ethinylestradiol.

In female mice initiated for liver carcinogenesis and exposed to unleaded gasoline, ethinylestradiol increased the number of altered hepatic foci; however, when given alone after the liver carcinogen, it reduced the number of spontaneous foci.

In female rats initiated for liver carcinogenesis, ethinylestradiol and mestranol increased the number of altered hepatic foci and the incidences of adenomas and carcinomas. Ethinylestradiol also increased the incidences of kidney adenomas, renal-cell carcinomas and liver carcinomas in male rats initiated with *N*-nitrosoethyl-*N*-hydroxyethylamine. In hamsters initiated with *N*-nitrosobis(2-oxopropyl)amine, ethinylestradiol increased the incidence of renal tumours and the multiplicity of dysplasias.

In female rabbits, subcutaneous administration of ethinylestradiol alone was associated with the proliferation of hepatic bile duct cells.

In female mice, subcutaneous administration of ethinylestradiol alone was associated with the development of uterine adenocarcinomas. In male hamsters, subcutaneous implantation of ethinylestradiol in combination with menadione was associated with the development of renal tumours of unspecified histology.

Oral administration of ethinylestradiol to p53-deficient female mice in combination with an intraperitoneal injection of the known carcinogen, *N*-ethyl-*N*-nitrosourea, increased the incidence of uterine atypical hyperplasias and stromal sarcomas.

Subcutaneous injection of estradiol induced uterine adenocarcinomas in female mice and subcutaneous implantation of estradiol induced renal tumours in male hamsters.

In female mice initiated with *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine, subcutaneous implantation of estradiol, estrone, estriol, 16β-hydroxyestrone diacetate, 16α-hydroxyestrone and 17-epiestrol increased the incidence of endometrial adenocarcinomas.

Progestogens

The incidence of pituitary adenomas was increased by norethisterone in female mice and by norethynodrel in female and male mice and male rats.

The incidence of malignant mammary tumours was increased in female mice by lynestrenol, megestrol acetate and norethynodrel. In female rats, lynestrenol and norethisterone slightly increased the incidence of malignant mammary tumours. Norethisterone also slightly increased the incidence of malignant mammary tumours in male rats, while norethynodrel increased the incidence of both benign and malignant mammary tumours in male rats. In female dogs, chlormadinone acetate, lynestrenol and megestrol acetate increased the incidence of benign and malignant mammary tumours; however, lynestrenol had a protective effect at a low dose, but enhanced tumour incidence at two higher doses. Levonorgestrel did not increase the incidence of mammary tumours in one study in dogs.

In female mice treated with 3-methylcholanthrene to induce uterine tumours, norethynodrel further increased the tumour incidence.

Megestrol acetate increased the incidence of liver adenomas in female mice. Cyproterone acetate increased the incidences of liver adenomas and hepatocellular carcinomas in female and male mice, but at doses exceeding the maximum tolerated dose. In rats, the incidence of liver adenomas was increased by norethisterone acetate (females and males), norethisterone (males), norethynodrel and cyproterone acetate (females and males).

The numbers of altered hepatic foci in female rats were also increased by norethisterone acetate and cyproterone acetate. In male mice treated with chlormadinone acetate, ethynodiol diacetate, lynestrenol, norethisterone or norethisterone acetate, the incidence of liver adenomas was increased. In female rats treated with *N*-nitrosodiethylamine to initiate hepatocarcinogenesis, norethynodrel increased the number of altered hepatic foci. Norethynodrel alone was shown to increase the incidence of hepatocarcinomas in male rats.

Levonorgestrel in combination with *N*-nitrosobis(2-oxopropyl)amine did not increase the incidence of renal dysplastic lesions or tumours in hamsters.

Oral administration of dienogest induced mammary gland proliferation in female dogs but not in female rats or monkeys.

5.4 Other relevant data

Absorption, distribution, metabolism, and excretion

Estrogenic and progestogenic compounds in oral contraceptives are readily absorbed and undergo metabolism to varying extents by bacterial enzymes, enzymes in the intestinal mucosa and especially those in the liver. The metabolism typically involves reduction, hydroxylation and conjugation. The so-called ‘first-pass’ through the liver reduces the overall bioavailability of oral contraceptives. Peak concentration levels in the systemic circulation are observed between 0.5 and 4 h after intake. Hydroxylated metabolites are usually conjugated as glucuronides or sulfates and are eliminated rapidly with half-lives of 8–24 h.

The formulations of combined hormonal contraceptives continue to evolve, especially with the introduction of new progestogens. In general, the chemical structure of a progestogen determines its relative binding affinities for the progesterone and other steroid receptors, as well as sex hormone-binding globulin, which determine its biological effects. The logic involved in the development of newly synthesized progestogens, such as dienogest and drospirenone, is that they are devoid of estrogenic, androgenic and antagonist effects.

Estrogens are described in the Monograph on Combined estrogen–progestogen menopausal therapy.

Receptor-mediated effects

Exposure to combined hormonal contraceptives increases the proliferation of human breast epithelial cells, as observed in biopsies and fine-needle aspirate samples collected during small randomized studies. Combined hormonal contraceptives have atrophic and anti-proliferative effects on the endometrium that are apparently independent of the regimen and the progestogen used. Ethinylestradiol plus levonorgestrel induces ovarian epithelial apoptosis in intact monkeys. Estrogen or progestogens may enhance human papillomavirus gene expression in the human cervix via progesterone-receptor mechanisms and hormone-response elements in the viral genome. In-vitro studies support this notion, and mechanisms other than those that are receptor-mediated may be involved. Experiments in transgenic mouse models that express human papillomavirus 16 genes in the cervix showed that estrogens can cause cervical cancer, probably via receptor-mediated processes. This effect was diminished after cessation of treatment with estrogen. Colon carcinogenesis in animal models is inhibited by estrogens and there is adequate evidence to suggest that estrogens have inhibitory effects on

colon cancer cells via estrogen receptor-β. Various studies document the possibility of complex interactions of combined hormonal contraceptives with hormonal systems. No data were available to the Working Group on time since cessation of treatment or duration of treatment.

Genetic and related effects

There is additional evidence to support the conjecture that certain estrogens function as directly acting genotoxins. These findings give further credence to the hypothesis that certain estrogens are carcinogenic through direct genotoxic effects in addition to their presumed action via a receptor-mediated mechanism. Some of the more recent genotoxicity data suggest that some progestogens used in combined hormonal contraceptives may also act as direct genotoxins. Few data were available that considered the effects of combined exposures to estrogens and progestogens.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of combined oral estrogen-progestogen contraceptives. This evaluation was made on the basis of increased risks for cancer of the breast among current and recent users only, for cancer of the cervix and for cancer of the liver in populations that are at low risk for hepatitis B viral infection.

There is *evidence suggesting lack of carcinogenicity* in humans for combined oral estrogen–progestogen contraceptives in the endometrium, ovary and colorectum. There is convincing evidence in humans for their protective effect against carcinogenicity in the endometrium and ovary.

There is *sufficient evidence* in experimental animals for the carcinogenicity of the combinations of ethinylestradiol plus ethynodiol diacetate, mestranol plus norethynodrel, ethinylestradiol plus levonorgestrel and estradiol plus levonorgestrel.

There is *sufficient evidence* in experimental animals for the carcinogenicity of the estrogens ethinylestradiol and mestranol.

There is *sufficient evidence* in experimental animals for the carcinogenicity of the progestogens norethynodrel and lynestrenol.

There is *limited evidence* in experimental animals for the carcinogenicity of the combinations of ethinylestradiol plus megestrol acetate, mestranol or ethinylestradiol plus chlormadinone acetate, mestranol plus ethynodiol diacetate, mestranol plus lynestrenol, mestranol or ethinylestradiol plus norethisterone and ethinylestradiol plus norgestrel.

There is *limited evidence* in experimental animals for the carcinogenicity of the progestogens chlormadinone acetate, cyproterone acetate, ethynodiol diacetate, megestrol acetate, norethisterone acetate and norethisterone.

There is *inadequate evidence* in experimental animals for the carcinogenicity of the progestogens levonorgestrel, norgestrel and dienogest.

Overall evaluation

Combined oral estrogen-progestogen contraceptives are *carcinogenic to humans (Group 1)*. There is also convincing evidence in humans that these agents confer a protective effect against cancer in the endometrium and ovary.

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