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EFFECTS OF ORAL CONTRACEPTION ON CARCINOGENESIS

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Summary. *Hormonal contraception as a cause of cancer apper as to be unlikely. In fact, protective effects against ovarian and endometrial cancer have been documented. There are conflicting reports concerning the risks of liver, cervix and breast cancer. The possibly increased risks that have been recorded in some studies are not large enough to outweigh or demand changes in current practice. The responsibility to provide balanced information about oral contraception rests on clinicians. Time spent directly educating patients regarding the benefits and risks of these modalities is well spent time.*

Key words: *Oral contraception, cancer, ovarium, endometrium, cervix, breast*

Introduction

Oral contraception (OC), mainly combined oral contraception, is widely used by young healthy women who expect their physicians to prescribe safe drugs which will not harm their health. The possible causal association between OC and various cancers has been a major concern. Findings regarding the long term health effect of OC are based primarily on studies of high dose formulations which contain 50 mcg ethinil estradiol or more.

Ovarian cancer

Newhouse et al (1977) were the first to suggested that OC might protect against ovarian cancer (1). The "incessant ovulation" hypothesis holds that a key step in the pathenogenesis of ovarian cancer is the disruption of ovarium epithelium occurring at the time of ovulation (2). A high lifetime total of ovulatory cycles may increase ovarian cancer risk (3). The major factors of anovulation during normal reproductive life are pregnancy, breast feeding and OC use.

OC use is associated with a powerful protective effect in reducing the risk of ovarian cancer. The available data suggest that OC use reduces the overall risk of ovarian cancer by 40% to 80%. Protection is noted after 3 to 6 months of use. It has been demonstrated with low dose preparations, increases with the duration of use and persists for 15 to 19 years following discontinuation (4).

The risk factors for ovarian cancer include nulliparity and positive family history. Recent advances in genetics have clarified the relationship between heredity and the ovarian cancer risk. The lifetime ovarian cancer risk for women with BECA 1 mutation is 45% and the risk for women carrying the BRCA 2 mutation is 25% (5).

Nulliparous women who used OC for at least 5 years reduced their risk of ovarian cancer to a level equal to or less than that expected by parous women who had never used OC. Women with a positive history of ovarian cancer who had used OC for 10 years or more reduced their risk to a similar or lower level that of women with a negative family history (6).

The Hereditary Ovarian Cancer Clinical Study Group examined the effect of OC use and ovarian cancer in this high-risk population. The large study included 207 women with ovarian cancer and 161 of their healthy sisters as controls. All women with ovarian cancer carried either the BRCA 1 (179 women) or BRCA 2 (28 women) mutation. The controls were enrolled regardless of whether they had the mutation. Past OC use conferred a 50% reduction in risk. Increasing duration of use reduced the risk to 60% after 6 or more years. Restricting the analysis to the controls positive for either BRCA mutation reduced the relative risk to 0.4 (60% reduction in risk). The risk reduction was similar for either mutation (5).

The profound protective effect has led to the consideration of OC use for chemioprevention of ovarian cancer in women at increased risk based on family history or genetic mutational risk assessment (7).

Endometrial cancer

Estrogen proliferation of endometrium combined with absent or inadequate progestional suppression characterizes the majority of women who develop endometrial cancer. In women who use OC the endometrium is almost continuously under the influence of synthetic progestogen.

The most plausible biological explanation for the protection effect by OCs is through their progestogen domination which suppresses endometrial mitotic activity (8). Oral contraception use is associated with a 40-50% decrease in risk of developing endometrial cancer. Protection conferred by OCs begins within one year of use and persists for at least 10 to 30 years after last OC use (9,10,11,12,13).

A meta analysis reviewed 10 case-control studies and one cohort study that addressed the effect of OC use on endometrial cancer (14). The results suggested an approximate 50% reduction in risk conferred by OC use. Protection increased with longer duration of use regarding from 56% after 4 years to 72% at 12 or more years. The protection decreased only slightly from 67% 5 years after last use to 49% 20 years after last use. OC use offered protection against all three major histologic types of endometrial cancer: adenocarcinoma, adenoacantoma and adenosqamous.

Women at higher risk for endometrial cancer should consider OC use even if the contraceptive effect is not required (4).

Cervical cancer

The primary underlaying cause of cervical cancer is human papilloma virus (HPV), a sexually transmitted infection. The age of the first intercourse and number of sexual partners are most likely indicators of risk of HPV exposure rather than independent risk factors.

Cervical sqamous cell cancer is the most common form. A lifetime number of male sexual partners and incidence of HPV-infection are positively associated with this cancer while the use of condom or diaphragm protect against this disease. Women who use OC often have more sexual partners and are less likely to use barrier contraception than the others (15). Evaluating results of this issue is challenging because number factors may influence development of cervical cancer and the disease develops slowly, over a long time period and can be largely prevented by periodic cervical citology (16).

Some studies failed to find a significant association between the risk of invasive cervical cancer and ever OC use (17,18,19).

The World Health Organisation (WHO) Collaborative Study of Neoplasia and Steroid Contraceptive found a statistically significant increased risk of invasive cervical cancer of 1.3 among ever users of OC. Risk was highest among women who had used OC for four or more years and it declined in the eight years after last use to that of non-users (20).

The Oxford Family Planning Association contraceptive study found that every OC use had a slightly higher overall risk of cervical cancer compared with never-users (relative risk 1.4) (16). On the other hand, this study showed that cervical neoplasia occurred more frequently in the OC users than in users of intrauterine contraceptive device and that preneoplastic lesions of cervix progressed more rapidly among OC users than among users of intrauterine contraceptive device (21).

Cervical adenocarcinoma account for approximately 10% of cervical cancers. They are not as easily detected as other lesions by cervical citology. The incidence appears to be increasing. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives found 1.5 relative risk of cervical adenocarcinoma among ever-users of OC. The risk increased with the duration of use and young age at first use. The risk was highest in current and recent users and declined with time since last use (22).

Because adenocarcinoma of the cervix is a rare the disease absolute risk is low.

Some studies have disscused the possible mechanism of OC action on cervical carcinogenesis. Eversion of cervical columnar epithelium with activation of the immature metaplastic process may increase the epithelia at risk (23). OC were shown the decreasing serum folate levels. These women have increased incidence of cervical intraepithelial neoplasia (CIN) and cervical cancer (24). Estrogens stimulate cytocine production of mucosa which may reduce susceptability to primary HPV infection (25). Beta estradiol increases transcription of the open reading frames of E6 and E7 in HPV infected women (26). Progesterone and progestogens seem to modulate expression of HPV gene in cervical keratocytes (27).

Until recently it was not clear whether OC increased the risk of cervical cancer independent of the risk attributable to HPV, whether they act as cofactors to HPV in cervical oncogenesis or the increased risk merely reflects secondary associations that are attributable to HPV infection.

One recent analysis did not show a significant increased risk for CIN 2 and 3 among women with a history of prolonged OC use since HPV was taken into account (28,29). The other large multicenter case control study found increased risk for carcinoma in situ (CIS) and cancer among OC users that was independent of HPV infection. This study evaluated the effect of OC use and HPV detection on the risk of cervical cancer compared with never-users. Women who used OC for less than 5 years did not have an increased risk of cervical cancer. Relative risk for women who had used OC for 5-9 years was 2.82 and for women who had used them for 10 years or longer was 4.03. The investigators concluded that long term OC use could be a cofactor that increase the risk of cervical cancer by up to fourfold in women who are positive for high risk of HPV infection (30).

The emphasized results raise the question of whether women with cervical precursor lesions should consider coming off OC or not. The evidence at this time does not seem to be sufficient to recommend that these women stop using OC but they should be under cytologic screening more frequently than other ones or these lesions should been threated. It would seem that OC may promote rather than initiate cervical neoplasia in women at risk (13).

Breast cancer

Breast tissue is responsive to ovarian hormones. DNA synthesis decreases during the first half of the normal menstrual cycle but after ovulation, when progesterone is synthetized, there is a marked rise in epithelial activity which depends on the prior exposure to estrogen. The hormonal effects of OC on breast are complex. On one hand, they cause protective anovulation, on the other hand, the mixture of estrogen and progestogen may stimulate mitotic activity in breast tissue (31). An increased incidence of breast cancer has occurred contemporaneously with the growing use of OC since their introduction in the early 1960s (32). Epidemiological and clinical studies indicate that this form of cancer is hormonal mediated. The possibility of a link between OC use and breast cancer has led to intensive research. Studies have provided inconsistent results causing controversy among investigators and confusion among clinicians.

Therefore, the Collaborative Group on Hormonal Factors in Breast Cancer was established in 1992 to collect and reanalyse the worldwide data related to breast cancer and OC use (33,34). The study involved a compilation of individual data on 53 297 women with breast cancer and 100 239 controls from 54 studies in 25 countries. The vast majority of women used OC. Progestogen-only pills were used 0.8% and progestogen-only injection 1.5% of study population (35).

The study found an overall relative risk of cancer associated with every use of 1.07. Current users and those who had used hormonal contraceptives within 10 years were at a slightly increased risk through risk declined progressively with time since last use and disappeared after 10 years. The relative risk in current users was 1.24 and in women who used hormonal contraception 1-4 years ago the relative risk was 1.15. For women who used them 5-9 years ago the relative risk was 1.07 and for women who used them 10-15 years ago relative risk was 0.98 (35).

Women who started using hormonal contraceptives before age 20 had a higher relative risk of breast cancer within five years of use than those who started later. Among women who used hormonal contraception through their 20s there is little difference in breast cancer incidence compared with non-users because of the low background incidence of breast cancer in this group. Among women who started use hormonal contraception until their 30s or 40s the incidence of breast cancer could be slightly elevated compared with non-users in the same age groups because the baseline incidence of breast cancer is higher in older women (35).

The Collaborative Group study demonstrated that hormonal contraception users who developed breast cancer had, in general, less advanced disease than those with breast cancer who never used this method of contraception (7). The hormonal contraception use was associated with a decreased risk of tumors that spread beyond the breast to auxiliary lymph nodes (relative risk 0.7) (35). One possible explanation for this finding is that hormonal contraceptive users receive more frequent and careful medical evaluation (36). The other possible explanation is that hormonal contraceptives may promote the growth of existing tumors rather than their likelihood to metastase (35).

The reanalyse clearly demonstrated that the characteristics of contraceptive use including estrogen dose, progestagen type and duration of use do not increase the risk of breast cancer (32).

Women with a family history of breast cancer are not at an additional risk over their already increased baseline risk (13,37). There is no evidence that a positive family history of breast cancer should be a contradiction to hormonal contraception use (36,13). A family history of breast cancer does not modify the effect of OC on risk of breast cancer in general but it may increase the risk in women with BRCA 1 and BRCA 2 mutations (34, 38).

Breast cancer is a common disease and on the increase. The use of hormonal contraceptives is also common and is expected to increase worldwide. In that way even a small increase in the risk of breast cancer in women using this method of contraception would be important because of the frequency of the exposure. The available data do not provide the conclusive answer that is need.

Colorectal cancer

An examination of the incidence of colorectal cancer in the Nurses" Health Study showed that the risk of developing colorectal cancer among women who used OC for 96 months or longer was 40% lower than among never-users (relative risk 0.6) (40). The trend for duration effect was significant. It is unclear whether protection accrues to users of low-dose pills because this cohort primarily reflects use of high-dose pills (41).

A large case control study conducted in Italy documented a 37% reduction in risk for cancer associated with OC use. Increasing duration of use decrease the risk further (42).

A possible biological explanation for the effect includes favourable changes induced by estrogen in bile synthesis and concentration in the colon. Estrogen receptors have been identified in colon epithelial cells and serve to inhibit cell proliferation as noted in vitro studies(40).

OC use also reduces the risk of colorectal adenomatous polyps, a premalignant lesion (40).

Liver cancer

Primary hepatocelular cancer is an exceptionally rare disease especially in young women. Its development in OC users has been reported but only very rarely (43). The evidence that OC may cause primary hepatocelular cancer has come from uncontrolled studies (44). However, a WHO study (1989) suggests that the current

patterns of OC use do not alter the risk of liver cancer in areas where hepatitis B is probably the main risk factor (13). The conclusion derived from WHO study supports the view that there is no increased risk of hepatic cancer associated with OC use even in countries with an increased prevalence of liver cancer (45).

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UTICAJ ORALNE KONTRACEPCIJE NA KARCINOGENEZU

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Kratak sadržaj: *Oralna kontracepcija verovatno nije uzrok pojave karcinoma. U stvari, dokumentovan je protektivni efekat u odnosu na pojavu ovarijalnog i endometrijalnog karcinoma. Prisutni su konfliktni izveštaji u odnosu na karcinom dojke, grlića materice i kolona. Moguće povećanje rizika koje je uočeno u nekim studijama nije dovoljno da bi imao značaj ili da bi zahtevao promenu u sadašnjoj praksi. Odgovornost za pružanje balansiranih informacija o oralnoj kontrcepciji je na kliničarima. Vreme provedeno za edukaciju pacijenata u pogledu beneficija i rizika je dobro utrošeno vreme.*

Ključne reči: *Oralna kontracepcija, ovarium, endometrijum, cerviks, dojka*