Histologic Changes Associated With Oral Contraceptive Usage

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ABSTRACT

Histologic changes associated with oral contraceptive usage have been described in the cervix, endometrium, myometrium, ovaries, breast, liver and blood vessels. Several types of lesions have been shown to occur frequently in women taking hormonal contraceptives. These include: (1) microglandular hyperplasia of the cervix; (2) endometrial gland regression and stromal decidualization (combination agents); (3) ovarian size reduction associated with cortical fibrosis, suppression of follicle growth and decreased luteinization; and (4) endothelial proliferation and subendothelial fibrosis in blood vessels generally. In addition, cases have begun to be reported in the past few years of adenocarcinoma of the cervix, carcinoma of the endometrium and tumors of the liver. Atypical but benign changes have also been described in myometrium and breast tissue, and neoplastic lesions in animals given hormonal contraceptive agents have been reported in these sites as well as in the ovary. The various types of changes that occur, both benign and malignant, correlate with known actions of the sex steroids.

Introduction

Oral contraceptive agents containing steroid hormones of estrogenic and progestational type have been in general use for approximately 15 years. During this time, there have been numerous reports on various side effects, particularly thromboembolic phenomena, diabetic-type changes, mental depression and breast changes. These adverse effects have resulted in some caution in the use of the oral contraceptives, but they have not been seen to be a serious deterrent to their continued use.

Histologic changes, especially those potentially associated with tumor formation, represent another area of concern, one with more obviously serious implications. The carcinogenic capacity of estrogenic compounds in animals is well known. However, it has generally been felt that clinical analogies could not be drawn from the animal studies and that concern about neoplastic changes resulting from oral contraceptive usage was unwarranted.

Recently, the unsettled nature of this problem has become increasingly evi-
Several reports have appeared implicating oral contraceptives in the development of proliferative histologic changes, benign and malignant, in various organs. Lesions have been described in the cervix, endometrium, myometrium, ovaries, breast, liver and blood vessels. It is the purpose of this report to review information currently available on histologic changes associated with oral contraceptive usage and to consider the possible implications.

**Cervix**

Quite early following the introduction of hormonal contraceptives, concern was raised about the possibility of a carcinogenic effect on the cervix. The prior introduction of the Papanicolaou smear for detecting preinvasive stages of cervical carcinoma provided an excellent tool for testing this possibility. Initial studies based on cytologic examinations indicated an increased incidence of squamous dysplasia and carcinoma *in situ* in users of oral contraceptives in comparison with those using no or other forms of contraception.\(^1,6,16,18,34,49\) Subsequent studies failed to document an effect of the oral contraceptives on the incidence of dysplasia, but rather indicated a higher incidence of dysplasia in pill choosers.\(^65\) Similarly, the injectable progestagens were found to have no effect on the incidence of new cases of carcinoma *in situ*.\(^14\) In a recent follow-up report, Melamed et al indicated that further extension of studies suggesting increased prevalence of carcinoma *in situ* in women using oral contraceptives compared with diaphragm users revealed no statistically significant differences between the two groups.\(^48\)

An important factor in the analysis of cytologic smears of oral contraceptive users is the associated effect on folate metabolism. Megaloblastic changes resulting from folic acid deficiency can be reflected in the cervical epithelium\(^37\) and may possibly be confused with dysplasia. Such a misinterpretation can be avoided if it is remembered that dysplasia is associated with irregular distribution of chromatin and nuclear hyperchromasia, while the megaloblastic effect of folic acid deficiency results in enlargement, but otherwise bland, homogeneous nuclei. Another point to be recognized is that there is an increased incidence of cervicitis in contraceptive users that may be responsible for cellular changes. The cytologic features of inflammation do not include irregular chromatin distribution and nuclear pleomorphism, such as occur with dysplasia.

While evidence for an effect of the oral contraceptives on the squamous epithelium of the cervix has not been established, an effect on the glandular epithelium is clear. A distinctive lesion of the cervix, involving glandular hyperplasia and polyp formation, has been noted to be present in a high percentage of pill users.\(^7,8,35,38,36,66\) In a few instances, these lesions were thought to represent adenocarcinoma, but clinical follow-up and reevaluation of the microscopic appearance indicated this not to be the case. The changes include microglandular hyperplasia, associated with squamous metaplasia, increased vascularity and neutrophilic infiltration, both in the stroma and within glands. The glands are lined by a single layer of epithelium which is uniform in appearance and thus malignancy can be excluded. Lesions of this type are found in 44 percent of oral contraceptive users,\(^53\) with the combination agents producing a slightly higher incidence than the sequentials.\(^25\) Similar changes have also been seen during pregnancy and post-partum and have been concluded to be an end-result of progesterone stimulation.\(^53\)

Although it is important to recognize that the microglandular hyperplasia described is a benign lesion, the possibility
that endocervical adenocarcinoma may occur in association with oral contraceptive usage must also be considered. A recent case report from Israel illustrates this point. A 35 year old woman who had been on combined contraceptive medication for the past four years developed a papillary lesion of the cervix. The microscopic appearance was that of a pleomorphic glandular neoplasm distinctly different from the benign hyperplastic lesions described and typical of an endocervical adenocarcinoma. That this case occurred in an Israeli-born Jewish woman, a member of a group with a very low incidence of cervical cancer, and followed several years of continuous medication, strongly suggests a causative relationship. Whether or not additional cases will be found remains to be seen, but it is important to be aware that such a relationship may exist.

**Endometrium**

The effects of contraceptive hormones on the endometrium have been well described. The combination drugs initially stimulate secretory changes in the glands, followed by glandular regression resulting in small, inactive glands embedded in a dense decidual stroma. The combination of narrow tubular glands and dense collections of plump decidualized stromal cells presents a characteristic appearance. The sequential drugs, on the other hand, produce a picture essentially similar to that of the normal menstrual cycle, except for a delay in the appearance of secretory changes. Both types of preparations elicit vascular changes, consisting of endothelial proliferation, smooth muscle hyperplasia and dilatation of sinusoids. In culture, the effects are similar to those in vivo, including prominent vascular changes and a swirling pattern of stromal cells around glands and blood vessels.

Electron microscopic studies have revealed nuclear and cytoplasmic changes in endometrial gland cells following administration of contraceptive steroids. The nucleolar channel system which normally appears in post-ovulatory endometrial glands, is prevented from developing, as are giant mitochondria normally seen in the secretory phase. In some cases, premature and asynchronous development of the endometrium is indicated by the presence of nucleolar canalicular structures and giant mitochondria in apparently proliferative glands.

Until recently, development of endometrial carcinoma in women taking oral contraceptives was not considered to be a problem, since the predominantly progestational effects of these agents would appear to be protective against stimulation of endometrial proliferation. However, in response to an apparent increase in endometrial cancer in women under 40, a Registry for Endometrial Carcinoma in Young Women Taking Oral Contraceptive Agents was established in November 1973. During the first 18 months, 21 cases were recorded, of which there were 10 adenocarcinomas, 5 adenoacanthomas, 2 mixed adenosquamous carcinomas, 1 clear cell carcinoma and 3 secretory carcinomas. Although this still constitutes a very small number of cases among the millions of oral contraceptive users, additional cases continue to be reported. Of note is the fact that the majority of cases thus far recorded have been in women using sequential agents. The significance of this observation will depend on analysis of further material.

Stromal proliferation in endometrial tissue has also been described in two patients taking oral contraceptives, but it was not clear whether these lesions were actually of neoplastic nature. In mice, administration of progesterone and 19-nor contraceptives over prolonged periods induced endometrial stromal sarcomas in 11 of 55 animals.
Myometrium

Myometrial hyperplasia has been associated with oral contraceptive usage. In addition, atypical leiomyomas, i.e., tumors with abnormal nuclei but without increased cellularity, myometrial hypertrophy and myometrial nodules, have been described following progestagen treatment.

Ovaries

Histologic changes in the ovaries following contraceptive administration include cortical fibrosis, follicle degeneration, decreased luteinization, cyst formation and increased vascularity. The overall size of the ovaries is reduced. A normal number of primary follicles is present, but large follicles are greatly reduced in number. These changes are reversible with restoration of follicle growth and maturation occurring after cessation of contraceptive administration.

Experimental studies in rhesus monkeys given oral contraceptives also demonstrated inhibition of follicle growth, cortical fibrosis and diminution in ovarian size; normal morphology was restored one to two months after the end of treatment. Similar changes were found in mice following long-term treatment with contraceptive steroids.

Granulosa cell tumors and nodular proliferation of lutein cells have been noted in mice after administration of injectable and oral progestogens. Such findings have not been reported in women taking oral or injectable contraceptives.

Breast

Considerable controversy has surrounded the question of a possible association between oral contraceptives and breast cancer. A vast amount of experimental data exists on the role of estrogens in the pathogenesis of cancer of the breast. This has led to caution in prescribing oral contraceptives for women at risk for developing breast cancer. Thus far, the estrogen-progestogen combinations used as contraceptives have not been shown to provoke carcinogenic effects in women. The assumption has been that the parallel effect of the progestogens protects against the potential carcinogenic effect of the estrogens. However, this assumption must be questioned in view of the suggested associations between oral contraceptives and neoplastic changes in other sites described elsewhere in this report.

Early studies indicated that fibroadenomas occurring in women taking hormonal contraceptives exhibit atypical changes, including haphazard arrangement of ducts and acini, intraluminal papillae, cribriform patterns and bizarre epithelial proliferation. Subsequent investigations determined that there was no difference in the incidence or histological appearance of fibroadenomas in oral contraceptive users and controls. Similarly, the various epithelial alterations associated with fibrocystic disease were qualitatively and quantitatively similar in the two groups. In an extensive retrospective study, it was reported that oral contraceptive use was not related to the risk of breast cancer and, in fact, may have a protective effect against formation of benign breast lesions.

No increase in the incidence of breast cancer in women under 35 has occurred following the introduction of oral contraceptives, and those cases that have developed in contraceptive users have been reported to show no difference in gross and microscopic features from those in young women not taking hormones. In another study, three cases of carcinoma of the breast occurring in women on hormonal contraceptives were found to have several unusual features including both lobular and ductal components, secretory activity and conspicuous mucopolysaccharides in the stroma of involved lobules and around neoplastic ducts.
Animal studies have continued to be performed in an attempt to clarify the oral contraceptive-breast cancer issue. Administration of an oral contraceptive to six rhesus monkeys resulted in the development of infiltrating duct carcinoma with extensive lung metastases, leading to death in one of the animals after 18 months of treatment. Earlier investigators described the appearance of breast nodules in dogs placed on a contraceptive regimen, but subsequent reports have doubted the relevance of these studies to the human female and have noted no increase in breast nodules in women receiving contraceptives. In view of the conflicting evidence and known carcinogenic potential of estrogenic hormones, it remains an open question whether or not oral contraceptives may play a role in the development of neoplastic changes in the breast.

Liver

Centrolobular congestion and mild cholestasis have been associated with oral contraceptive usage. In addition, several reports have appeared in the past few years describing the occurrence of liver tumors and hyperplastic changes in women taking oral contraceptives. This is a striking finding in view of the rarity of hepatic tumors in young women. A spectrum of lesions has been described, ranging from focal nodular hyperplasia to benign hepatoma to hepatocellular carcinoma. Both the benign and malignant tumors have been associated with severe intraperitoneal hemorrhage causing death in several cases. Vascular changes appear to be responsible for the frequent massive hemorrhage provoked by these lesions and are thought to play an etiologic role. The association of liver tumors with oral contraceptives is a cogent illustration of the wide-ranging effect of sex steroids on various tissues, including those outside the reproductive system.

Vascular

Besides the blood vessel changes already described, vascular alterations in various tissues have been noted in contraceptive users. Examination of the blood vessels of women who developed thromboembolic disorders revealed endothelial proliferation and subendothelial fibrosis in arteries and veins of women taking oral contraceptives, but not in those who were not using these agents. The lesions were characterized by structural and histological changes in the intima and media. These changes paralleled the development of endometrial and ovarian changes associated with contraceptive usage.

Discussion

The principal histologic changes related to hormonal contraceptive administration are summarized in table I. The variety of changes encountered can be explained on the basis of known effects of the sex steroids. These effects are a result of the direct action of estrogenic or progestational compounds on particular target tissues or of indirect actions of the hormones.

In the cervix, the sex steroids are known to act on the endocervical epithelium to promote glandular proliferation and

<table>
<thead>
<tr>
<th>Site</th>
<th>Changes</th>
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<tbody>
<tr>
<td>Cervix</td>
<td>Microglandular hyperplasia; squamous metaplasia, neutrophilic infiltration, increased vascularity</td>
</tr>
<tr>
<td>Endometrium</td>
<td>Glandular regression and decidualized stromas (combination)</td>
</tr>
<tr>
<td></td>
<td>Normal cyclic pattern with delayed secretory phase (sequential)</td>
</tr>
<tr>
<td>Myometrium</td>
<td>Hyperplasia, atypical leiomyomas, myometrial nodules</td>
</tr>
<tr>
<td>Ovaries</td>
<td>Reduced size, cortical fibrosis, inhibition of follicle maturation, decreased luteinization</td>
</tr>
<tr>
<td>Breast</td>
<td>Florid fibroadenomas (?)</td>
</tr>
<tr>
<td>Liver</td>
<td>Centrolobular congestion, cholestasis; nodular hyperplasia, hepatoma</td>
</tr>
<tr>
<td>Vascular</td>
<td>Endothelial proliferation, subendothelial fibrosis</td>
</tr>
</tbody>
</table>
mucus production. It is therefore not surprising that usage of contraceptive agents can result in glandular hyperplasia. On the other hand, the principal effects of the sex steroids on the squamous epithelium of the cervix and vagina are related to epithelial maturation rather than proliferation, and thus an association of hormonal contraceptives with squamous lesions, e.g., dysplasia, carcinoma in situ, would not be expected, which has thus far proven to be the case.

The actions of estrogen and progesterone on the normal endometrium are well known, and the corresponding effects of the combination and sequential agents on the endometrium are easily explained by an understanding of these actions. With the combination agents, stimulation of glandular proliferation by estrogen is suppressed by the accompanying progestogen which also evokes a decidual change in the stroma, resulting in the characteristic appearance of glandular regression and decidualized stroma. Sequential administration more closely mimics the normal cyclic pattern of hormone secretion and thus produces a relatively unaltered histologic appearance, except for a slight delay in the development of secretory changes. Since estrogenic stimulation is associated with glandular proliferation, it is not unreasonable to suspect that exogenous estrogens might provoke excessive glandular proliferation and possibly neoplastic change, i.e., adenocarcinoma. That this may in fact take place is suggested by the occurrence of endometrial carcinoma in association with contraceptive usage, and particularly with sequential administration where there is an initial phase of estrogen alone.

The changes in the ovaries appear to be a result of the suppressive effect of contraceptive steroids on pituitary gonadotropin secretion. This is consistent with the well recognized negative feedback effect of the sex steroids on gonadotropin production. Decrease in gonadotropin levels results in inhibition of follicle maturation and luteinization as well as consequent reduction in ovarian size.

Effects of the contraceptive agents on breast tissue are less clear. The relative roles of estrogen, progesterone and other hormones, such as prolactin, in the pathogenesis of breast neoplasia remain to be determined. Further work is needed before implicating or denying a role for oral contraceptives in the development of histologic changes in breast tissue.

Also unclear is the manner in which contraceptive agents might induce proliferative changes in liver cells. The suggestion has been made that vascular alterations could be responsible. This explanation would be in line with the known effects of the sex steroids on vascular tissue and the indications that interference with blood supply contributes to the development of hepatic lesions.

Evidence for an association of hormonal contraceptives with neoplastic changes in the various sites described is summarized in table II. It should be stressed that the extent to which oral contraceptives are capable of provoking histologic changes may be just beginning to emerge. As Hertz has previously

<table>
<thead>
<tr>
<th>Type</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>Cervical adenocarcinoma</td>
<td>Single case report^13</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>21 cases on file in Registry^61</td>
</tr>
<tr>
<td>Endometrial stromal sarcoma</td>
<td>Animal studies^39</td>
</tr>
<tr>
<td>Myometrial tumors</td>
<td>Reports of atypical leiomyomas, myometrial nodules^19,^62</td>
</tr>
<tr>
<td>Ovarian tumors</td>
<td>Animal studies^38,^46</td>
</tr>
<tr>
<td>Breast tumors</td>
<td>Animal studies^33; possible association with atypical fibroadenomas^6,^26,^70</td>
</tr>
<tr>
<td>Liver tumors</td>
<td>Multiple case reports of hepatomas^1,^2,^9,^11,^32,^35</td>
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pointed out, a latency period in the range of 10 to 20 years must be assumed for the long-term effects of most agents. With the limited number of cases thus far described and an elapsed use period of approximately 15 years, further time is needed to assess adequately the capacity of the contraceptive agents to induce significant tissue alterations.

References


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