

# Hepatic Adenoma and Oral Contraceptive Use

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**H**epatic adenoma, once a rare neoplasm, has become increasingly common in recent years and is thought to be linked to long-term oral contraceptive use. Hepatic adenomas most often present catastrophically with severe abdominal pain arising from rupture and hemorrhage of the tumor into the abdominal cavity. The estimated annual incidence of hepatic adenoma is now greater than 3.4 cases per 100,000 oral contraceptive users, or about 320 new cases each year.<sup>1</sup> This report describes a case of hepatic adenoma serendipitously discovered during routine examination for renewal of an oral contraceptive prescription. The discussion focuses on early detection and appropriate management.

## CASE REPORT

A 36-year-old woman was seen in the spring of 1988 as a recently enrolled patient in a health maintenance organization. Her last gynecologic examination had occurred seven months prior to this visit, and findings on physical examination and Papanicolaou smear were reported to be normal. The patient had started to take oral contraceptives 20 years before. For approximately 14 years she took Norinyl 1 + 50, then two years prior to her visit she had changed to Ortho Novum 1 + 35. There was no family history of gynecologic abnormalities. The patient had a series of approximately 16 Papanicolaou smears. Atypical findings were found on one Papanicolaou smear five years ago, which was thought to be due to inflammation, and it was followed by four normal Papanicolaou smears. Her menses were regular on contraceptive pills, and she reported no problems with headache, elevated blood pressure, or leg pain. She had never smoked cigarettes. The patient reported no other health problems. In spite of her recent examination the patient elected to have a gynecologic

examination to prevent the need for another visit in the fall for oral contraceptive refills.

Routine examination was normal except that on palpation there was an asymptomatic, 10 × 11-cm palpable mass in the right upper quadrant of her abdomen. Computed tomography of the abdomen with and without contrast showed a large liver mass with extension below the pelvic rim. The study was not diagnostic, and a wide-ranging differential diagnosis was suggested. Celiac and hepatic arteriograms showed a large hypervascular tumor arising from the right lobe of the liver supplied by the right hepatic artery. A variant anatomy of the liver vasculature was noted, and the portal vein was not significantly involved. Partial right ureteral obstruction was also indicated by the arteriogram. On the following day tissue was obtained by transjugular liver biopsy; the specimen was consistent with hepatic adenoma, but the pathologist could not completely exclude the possibility of focal nodular hyperplasia of the liver from the biopsy specimen.

Because of the size of the lesion as well as the likelihood of hepatic adenoma, a laparotomy was carried out. A lobulated mass surrounded by a thick capsule measuring approximately 9 × 11 × 6-cm was found attached to the right lobe of the liver. It was removed without difficulty. Microscopic examination demonstrated multiple vascular structures amid proliferating hepatocytes lacking portal triads. Focal areas of hemorrhage were also noted. These findings were consistent with hepatic adenoma.

The postoperative course was uncomplicated, and oral contraceptive pills were discontinued.

## DISCUSSION

The rising incidence of hepatic adenomas in women using oral contraceptives was first reported in the early 1970s,<sup>2</sup> when such tumors were considered quite rare. Hepatic adenoma is easily confused with focal nodular hyperplasia, and authors have used a variety of terms to describe both. The two tumors are now easily distinguishable by gross and microscopic examination.<sup>3,4</sup> Clinically, focal nodular hyperplasia is not associated with menses or oral contraceptive drugs; both associations exist for hepatic adenoma.

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Both tumors may present with abdominal pain, but hepatic adenoma has a much larger vascular component that is more likely to present with hemorrhage and shock.<sup>5</sup>

Hepatic adenomas are now primarily found in women of reproductive age, whereas focal nodular hyperplasia occurs in all ages. Ninety-five percent of hepatic adenomas and 60 percent of focal nodular hyperplasias occur in women. Hepatic adenoma is almost always associated with oral contraceptive use.<sup>5</sup> Several independent studies supported a causal association between prolonged use of oral contraceptives and development of hepatic adenoma.<sup>1,5,6</sup> No careful studies of association between oral contraceptive use and development of focal nodular hyperplasia have been done, but the association seems to be no more than would be expected by chance alone.

Most patients with hepatic adenoma are symptomatic at the time of diagnosis. In Klatsken's series of 79 patients,<sup>7</sup> 41 percent presented with abdominal pain, tumor rupture, hemoperitoneum, and shock; 27 percent presented with abdominal pain from tumor hemorrhage. Another series showed 44 percent of 69 patients presenting with tumor rupture or hemorrhage.<sup>8</sup> In contrast to this threatening clinical course, patients with focal nodular hyperplasia generally have no symptoms and the prognosis is excellent. Ishak and Rabin<sup>3</sup> reported that 80 percent of cases of focal nodular hyperplasia were incidental findings in their series of 130 patients.

Routine laboratory studies are of little help in establishing the diagnosis. Hepatic adenomas arise from normal liver tissue, and routine liver function tests are usually normal even with very large tumors. Although no well-documented reports about the efficacy of ultrasonography in benign liver tumors are available, much more experience with technetium 99m sulfur colloid liver scans exists. The sensitivity of this scan for both types of tumors is only 70 to 80 percent, a disappointing yield for such large tumors. Abdominal computed tomography may be more helpful; tumors appear as low-density mass lesions, and areas of hemorrhage are common in hepatic adenoma. The sensitivity and specificity of abdominal computed tomography for these tumors is still under study, however.<sup>5</sup>

Hepatic arteriography is most valuable in the assessment of hepatic adenoma. The tumor generally appears as a hypervascular mass (or masses) with a dense capillary blush.<sup>7</sup> The most helpful finding is a visible septation of the tumor mass during the capillary phase, suggesting focal nodular hyperplasia. Since tumors can be differentiated in only 50 percent of the cases, many require further intervention for definitive diagnosis and treatment.<sup>5</sup>

The great majority of patients will require biopsy or excision of the lesion for therapy or definitive diagnosis. Needle biopsy may be more useful for lesions that are highly likely to be focal nodular hyperplasia, since hepatic adenoma has a large vascular component, and biopsy is more likely to be complicated by hemorrhage. Transjugular

liver biopsy is a relatively new technique requiring a high degree of technical skill. In this case tissue was obtained but the specimen was nondiagnostic. Had the specimen been identified as focal nodular hyperplasia, surgery could have been delayed or even avoided. An open surgical procedure is ultimately recommended in many cases.

While patients with focal nodular hyperplasia need no further investigation, and their tumors often regress with cessation of oral contraceptive pills, there is no question that detection of hepatic adenoma before rupture improves the outcome.<sup>1</sup> This tumor must be suspected in women taking oral contraceptive pills for three years or longer, especially with abdominal pain, and in those taking contraceptive pills who have any suggestion of hepatomegaly or mass on physical examination.

The overall mortality of hepatic adenoma is 8 percent,<sup>7</sup> with nearly all deaths resulting from tumor rupture or hemorrhage. Patients with no contraindications with or without symptoms should have surgical resection of hepatic adenoma because of the frequent complications experienced. Patients who are poor surgical candidates or who have minimal symptoms and physical findings may elect to discontinue oral contraceptive pills with very close follow-up. Unfortunately some tumors fail to regress, and a few even enlarge after withdrawal of oral contraceptives.

Both types of tumor may regress with cessation of contraceptive pills. After resection, oral contraceptive pills are contraindicated because the tumor recurrence rate is greater than 10 percent in patients who continue to use these agents.<sup>1,7</sup> The prognosis with removal of hepatic adenoma is excellent otherwise. Since estrogens are thought to be the factor promoting tumor formation in the liver, pregnancy in patients recovering from hepatic adenoma is also not recommended by some authors.<sup>9,10</sup>

Because of increasing but still rare reports of hepatocellular carcinoma in a few of these patients, Kerlin et al<sup>11</sup> now recommend elective laparotomy for diagnosis in all patients. Hepatic adenomas would still be resected if at all possible, and intraoperative wedge biopsy would be used to look for cancer in patients with focal nodular hyperplasia. Contraceptives have also been implicated in the development of hepatocellular carcinoma.<sup>12</sup>

Careful examination of the high-risk group offers the best and most economical way of preventing serious morbidity from hepatic adenoma. The index of suspicion for hepatic adenoma should increase with each year of oral contraceptive use. A simple but careful abdominal examination should be a part of each visit for renewal of oral contraceptives.

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