# Regression of multiple hepatocellular adenomas after cessation of oral contraceptive pills: a case report and review of the current literature

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## Abstract

**Hepatocellular adenoma (HCA) is an uncommon benign liver neoplasm usually solitary and identified incidentally on imaging. We report a case of a 50-year old female who was diagnosed with multiple hepatic adenomas of the inflammatory subtype. After discontinuation of oral contraception a decrease of both the number and size of the liver lesions was seen on magnetic resonance imaging (MRI) without the need of further intervention. The major challenge in the clinical management of patients with multiple HCAs resides in the risk assessment for future complications. In the case of multiple HCAs subtype seemed to be more relevant than the actual number of lesions. Because little is known about the natural evolution in patients with multiple HCAs, we performed a review of the current literature with focus on the different subtypes and their clinical relevance.** (Acta gastroenterol. belg., **2021**, 84, **505-508**).

**Key words**: Hepatic adenomatosis, oral contraception, conservative management.

## Introduction

Hepatocellular adenoma (HCA) is a rare benign liver lesion with a prevalence between 0.001 and 0.004%, predominantly seen in young and middle-aged women (1). There is a remarkable association with oral contraceptive pills (OCP), androgens, anabolic steroids and obesity (1-4). Despite their benign pathologic characteristics, adenomas can bleed or evolve into liver cancer, which is determined by size and/or molecular subtype. Risk factors and molecular subtypes are represented in table 1 (1-2, 5-7).

HCA usually presents as a solitary lesion, but in this case study we will focus on hepatic adenomatosis. This term was first suggested in 1985 by Flejou for the presence of 10 or more adenomas in an otherwise normal liver (5). Since then, more insights have been gathered regarding several subtypes of HCA. This has fueled the debate concerning the optimal management of multiple HCAs.

## Case history

A 50-year old women was referred because of the presence of multiple hypervascular liver lesions detected on a computed tomography. The patient underwent a cholecystectomy and appendectomy in the remote past and she was recently diagnosed with diabetes mellitus type 2. She was under OCP because of hypermenorrhea since 32 years. At the age of 33, she gave birth after an uncomplicated pregnancy. Her physical examination was unremarkable. Her body mass index was 27.1 kg/m².

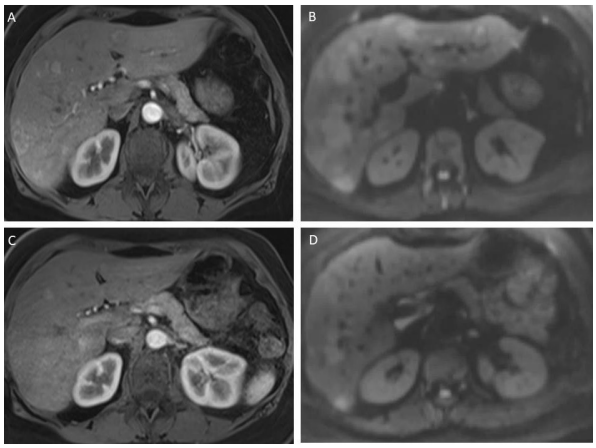


Fig. 1. — Upper row : multiple nodular liver lesions at (A) arterial phase contrast-enhanced MRI and (B) diffusion-weighted MRI compatible with liver adenomas.
Lower row : After withdrawal of hormone usage there is a partial regression of the lesions at (C) arterial phase contrast-enhanced MRI and (D) diffusion-weighted MRI

Laboratory investigation revealed an elevated C-reactive protein (31.2 mg/L, normal < 5 mg/L), serum alkaline phosphate (168 U/L, normal 38-126 U/L). Her full blood count, electrolytes, renal function and the other liver function tests were normal.

MRI showed multiple lesions (> 20) with lesion size ranging between 0.5 and 4.5 cm (figure 1A and 1B). The lesions showed arterial enhancement with persistent enhancement in the venous phase and only moderate signal intensity at diffusion-weighted imaging with b-value of 1000 s/mm2. A biopsy of a liver lesion showed hepatocytes without portal tract elements but with the presence of bile ductules and intralesional inflammatory infiltration. Steatosis was limited. Staining for amyloid A was positive confirming the diagnosis of a

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Table 1. — **The molecular subtypes of HCA linked with their epidemiology, clinical presentation and risk of complications**

| Subtype | Frequency | Gender | Risk factors | Pathology | IHC | Complications |
|---|---|---|---|---|---|---|
| HNF-1α inactivated HCA | 40-50% | Almost exclusively in women | HNF-1α germline mutation | Steatosis ++ | Absent L-FABP | Least aggressive in tumours < 5 cm |
| ß-catenin activated HCA<br>• mutation in exon 3<br>• mutation in exon 7/8 | 10%<br>5% | More frequent in men<br>/ | Glycogen storage disease, androgen use<br>/ | Cellular atypia, pseudoglandular formation, cholestasis | ß-catenin nuclear +ve GS +ve (diffuse)<br>ß-catenin nuclear -ve GS +ve (heterogenous) | Malignant transformation +++<br>No higher risk of malignant transformation |
| Inflammatory HCA | 35-45% | Predominantly seen in women | Obesity, alcohol, estrogen | Inflammatory infiltrates, ductular reaction, sinusoidal dilatation | SAA +ve<br>CRP +ve | Bleeding +++ |
| Sonic hedgehog activated HCA | 5% | | Obesity, estrogen | Contain often haemorrhagic foci | | Bleeding ++ |
| Unclassified HCA | 7% | | | | | |
| Mixed inflammatory HCA with activated ß-catenin<br>• mutation in exon 3<br>• mutation in exon 7/8 | 6%<br>4% | | | | | Malignant transformation +++ |

HCA, hepatocellular adenoma ; HNF-1α, hepatocyte nuclear factor-1 alpha ; L-FABP, liver fatty acid binding protein ; glutamine synthetase ; SAA, serum amyloid A ; CRP, C-reactive protein.




Figure 2. — Upper row : Normal portal tract and surrounding parenchyma (A). Lesion with sinusoidal dilatation and congestion, no cellular or nuclear atypia, no steatosis (B) (H&E, magnification 100x).
Lower row : Glutamin synthetase stain shows normal centrolobular staining in the surrounding parenchyma (left lower part), but negativity in the lesion (upper left part of the figure) (C)). Amyloid A stains shows positivity on multiple larger and smaller lesions. Here a lesion is shown (left side of the figure) while the surrounding is negative (right side of the figure) (D).

hepatic adenoma of the inflammatory subtype. Staining for glutamine synthetase was negative, excluding beta-catenin activity (figure 2) (3). The cessation of OCP use and weight reduction was advised. Six months after OCP discontinuation and a weight loss of 8.5 kg (BMI 24.3 kg/m²) a spectacular decrease of both the number and size of the liver lesions was seen on MRI (figure 1C and 1D). We also noticed a decline of C-reactive protein to 11.8 mg/L (normal < 5 mg/L).

## Discussion

We presented the case of a middle-aged women with multiple hepatic adenomas of the inflammatory type that regressed following cessation of OCP use and weight loss.

In our case, the fact that all lesions in the liver shared the same imaging characteristics and showed a similar shrinkage, suggests that all the lesions were of the same subtype. This is expected, although not always the case. A recent long-term observational study of patients with adenomatosis demonstrated an important heterogeneity with different subtypes in 29.4% of patients (8). As it is not feasible to biopsy all lesions in case of multiple HCAs, MRI may help to detect those lesions that are at risk for complications. The presence of fat and telangiectatic features are two MRI patterns specific for 2 major subtypes, hepatocyte nuclear factor-1 alpha inactivated HCA (H-HCA) and inflammatory HCA (I-HCA), respectively (1,9). However, as imaging is not always able to pick out the beta-catenin activated subtypes, we may consider a biopsy, especially of the lesions that are large,

Table 2. — **Overview of the current literature about the evolution in patients with multiple HCAs from different subtypess**

| | Number of patients with multiple HCAs (n > 2) | Subtypes (n or %) | Number of patients taking OCP | Duration of OCP use | Management other than stop OCP (n) | Follow-up | Long-term follow-up (%) |
|---|---|---|---|---|---|---|---|
| Dokmak, et al. 2009 (11) | 60 | • HNF-1α-inactivated (25)<br>• Inflammatory (27)<br>• Unclassified (8) | 49 | 61% > 10 years | • Surgical biopsy (3)<br>• Partial liver resection (56)<br>• Liver transplantation (1) | 70 months (mean) | • Stable disease (83%)<br>• Recurrence or progression (15%)<br>• Regression (9%) |
| Shao, et al. 2018 (10)* | 35 | • HNF-1α-inactivated (12)<br>• Inflammatory (8)<br>• Unclassified (1) | 36 | NA | None | 43 months (mean) | • Stable disease (58%)<br>• Progression (4%)<br>• Regression (37%)<br>• Disappearance (2%) |
| Barbier, et al. 2019 (8) | 40 | • HNF-1α-inactivated (46%)<br>• Inflammatory (31%)<br>• Sonic hedgehog (3%)<br>• Unclassified (8%)<br>• Mixed (15%) | 33 | 1-31 years | • Major hepatectomy (6)<br>• Minor hepatectomy or atypical liver resection (26)<br>• Biopsy (9)<br>• Hemostasis (3)<br>• Liver transplantation (1) | 10,6 months (median) | • Stable disease (46,7%)<br>• Progression (23,3%)<br>• Regression (30%) |
| Gonçalves, et al. 2020 (5) | 1 | • Inflammatory, without ß-catenin mutation | 1 | 17 years | None | 6 months | • Stable disease<br>• Normalisation of inflammatory markers and AP |
| Klompenhouwer, et al. 2020 (12)† | 134 | • HNF-1α-inactivated (18)<br>• Inflammatory (69)<br>• ß-catenin activated (2)<br>• Inflammatory with activated ß-catenin (3)<br>• Unclassified (10)<br>• HNF 1A-inactivated + inflammatory (2)<br>• Unknown (30) | 116 | NA | • Segment resection (82)<br>• Hemihepatectomy (44)<br>• Enucleation (8) | 49 months (median) | • Stable disease (62%)<br>• Progression (11%)<br>• Regression (25%)<br>• New lesion (2%) |

HCA, hepatocellular adenoma ; OCP, oral contraceptive pills ; HNF-1α, hepatocyte nuclear factor-1 alpha ; AP, alkaline phosphatase. * Including data of 9 patients with single HCA. † Evaluation of the effect of OCP withdrawal on the residual adenomas in the remnant liver after surgical resection in all patients.

growing or arising in male patients (who are more at risk for malignant transformation irrespective of size) (1,4). The risks of bleeding and malignant transformation are estimated to be 5% and 2% respectively in small HCA (< 5 cm) and 25% and 9%, for HCA > 5 cm (10). There is no difference between single HCAs or multiple HCAs (11). So, for multiple HCAs it seems rational to deal with these lesions as in the guidelines for single adenomas, where resection is recommended in symptomatic patients, for lesions ≥ 5 cm on baseline imaging or increased in size (≥ 1cm) on serial imaging (1) and for any lesion irrespective of size in male patients. However, in the case of multiple HCAs, technical aspects like the number of affected segments and evaluation of the remaining parenchyma should be taken into account. For small adenomas in women a conservative approach with cessation of OCP and weight reduction can be advocated (1).

The association between the use of OCP and the development of HCA and an increased risk of bleeding is well described and seems to be dose-dependent (6). Compared to single HCAs the development of multiple HCAs are more frequently seen in OCP users and in patients with obesity and steatosis (10).

There is evidence about regression of a single HCA upon withdrawal of OCP, but the natural history of multiple HCAs is poorly described in the literature. Furthermore, most series included both single and multiple HCAs which complicates the interpretation. An overview of the current literature about the evolution of multiple HCAs and correlation with the different subtypes is presented in table 2 (5, 8, 10-12). Information about the impact of OCP withdrawal on the different subtypes is scarce. A retrospective study of 44 patients by Shao *et al* (10), indicated that lesions with important fat infiltration (characteristic for H-HCA) showed a significant less size decrease after OCP cessation compared to those without fat infiltration. The team of Klompenhouwer *et al* (13) found a difference for HCA regression in different subtypes, in favour of I-HCA and unclassified HCA, although in a retrospective study of 134 patients no statistically significant differences could be found (12).

Interpretation of the effect of cessation of OCP may be confounded if other therapies (like resection or embolization ) are applied. The locoregional therapies may induce growth of the residual HCAs. A recent retrospective study by Klompenhouwer *et al* (12), of 134 patients with multiple HCAs (with 52 % I-HCA and 87% on oral contraceptives), evaluated the effect on the remaining lesions in the remnant liver after resection. After a median follow-up of 6 months they reported a regression in 24.6% of patients, stable disease in 61.9%, progression in 11.2% and in 2.2% new lesions developed. The authors suggested that the regression of the remaining HCAs could be secondary to the discontinuation of OCP or a result of weight loss, or by the change in tissue environment in the liver after resection of the largest lesion(s). When a conservative approach is adopted, surveillance is important because lesions can increase in size despite lifestyle change (1). Time and duration of surveillance depends on the molecular subtype, the evolution over time as well as the age of the patient. Discussion by an expert team is recommended.

In conclusion, the risk assessment of multiple HCAs should be based on size, tumor growth, gender and especially molecular subtype (based on MRI features and histology). The indication for surgical therapy of multiple HCAs should follow the guidelines as set for single HCAs with the consideration of technical difficulties.

## Conflict of interest

None

## References


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