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Review article

Hepatic complications of oral contraceptive pills and estrogen on MRI: Controversies and update - Adenoma and beyond☆

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ABSTRACT

Hepatic complications of oral contraceptive pills and exogenous estrogens include intrahepatic canalicular cholestasis, neoplasm formation and vascular pathologies. While it remains controversial as to whether estrogen plays a role in focal nodular hyperplasia, hemangioma or hamartoma, exposure to oral contraceptive pills and estrogen has a strong association with hepatic adenomas. Four different subgroups of adenomas have been described: Inflammatory, HNF-1α-mutated, β-catenin-mutated and unclassified. Vascular complications may include Budd-Chiari syndrome, vascular thrombosis, dilated sinusoids and peliosis.

1. Introduction

Oral contraceptive pills (OCP) are the most commonly used reversible means of birth control in women. Studies have shown an association between the use of oral contraceptive pills and cholestasis, hepatic neoplasms, as well as vascular pathologies. Acute intrahepatic canalicular cholestasis usually develops 2 to 3 months after starting OCPs and resolves after cessation. Patients with OCP-induced cholestasis often have a history of idiopathic cholestasis of pregnancy, and there is an underlying genetic component involving the bile salt export pump (BSEP) and ATP-binding cassette sub-family B 11 member gene (ABC B11) [1].

Women have been cautioned to avoid use of oral contraceptive pills in certain clinical conditions, which may include [2]:

a) Previous personal episode of cholestatic jaundice of pregnancy,
b) Those who have first-degree relatives with cholestasis of pregnancy or oral contraceptive-induced cholestasis,
c) Current or previous benign or malignant hepatic tumors,
d) Active hepatitis,
e) Diagnosis of familial defects of biliary excretion (Dubin-Johnson syndrome, Rotor's syndrome), and
f) Individuals with benign intrahepatic recurrent cholestasis.

OCPs have a known association with benign hepatic neoplasms such as adenomas and may rarely induce malignant transformation. Vascular complications are often seen with co-existing risk factors such as Protein C, Protein S deficiency, or Factor V Leiden mutations predisposing to venous thrombosis.

Fortuitously, these complications are rare and may be decreasing due to lower-dose OCPs use compared to decades ago. Nevertheless, it is important to recognize complications in a timely fashion, to avoid life-threatening events.

Abbreviations: OCP, oral contraceptive pills; HCA, hepatocellular adenomas; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; BCS, Budd Chiari syndrome

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2. Cholestasis due to OCP

Cholestasis appears to be related to estrogen effects on orphan nuclear receptors that modulate bilirubin metabolism, resulting in inhibition of bilirubin secretion into the biliary tree [3].

The reported frequency of cholestasis in these patients is 2.5 per 10,000 [4]. Moderate increase in risk, up to 50%, is seen in patients with a prior history of cholestasis of pregnancy [4]. Clinical presentation includes mild prodromal symptoms such as anorexia and nausea, followed by pruritus, which usually develop 2 to 3 months after starting OCPs. Moderately elevated serum alkaline phosphatase is often revealed on laboratory investigation. Progression to chronic cholestasis is extremely rare, and recovery typically occurs within days to weeks after cessation of this medication. Hormone replacement therapy (HRT) may similarly increase bilirubin levels, and monitoring of liver function tests (LFTs) is advisable. The primary role of imaging in this situation is to exclude gallbladder stones and other structural causes of obstructive jaundice. Otherwise, imaging is unremarkable.

2.1. Dubin-Johnson syndrome

Dubin-Johnson syndrome is of autosomal recessive inheritance with mutation in the ABCC2 gene resulting in defective transport of bilirubin from the hepatocytes into bile ducts, which consequently leads to a rise in serum conjugated bilirubin levels. It is often asymptomatic but may manifest only during pregnancy or with use of oral contraceptives. OCP use can impair hepatic excretory function and can transform a mild hyperbilirubinemia into frank jaundice [5]. Typically, imaging is unremarkable and shows no cause of obstructive jaundice.

3. Hepatocellular adenoma

Hepatocellular adenomas (HCA) have been traditionally described as neoplasms that occur in women taking oral contraceptives. Adenomas are now understood to represent a heterogeneous set of genetically disparate tumors with different genetic abnormalities and variable clinical and prognostic features. Lately, the Bordeaux group recognized a new molecular and pathologic classification of HCA (Table 1). According to genotypic and phenotypic characteristics and clinical features, estrogen-induced HCA is broadly divided into four different subgroups including inflammatory, Hepatocyte Nuclear Factor (HNF)-1α-mutated, β-catenin-mutated and unclassified [6,7].

The diagnosis of adenoma is usually made on imaging. Biopsy is usually neither recommended to make a diagnosis of adenoma (unless imaging is nonconclusive) nor to determine histological subtype [8,9].

3.1. Inflammatory subtype

Inflammatory HCA is the most common subtype of HCA, comprising 40–50% of all adenomas. These are classically seen in young women with a history of OCP usage (> 90%), in obese patients, and in those with underlying hepatic steatosis, diabetes mellitus, alcohol abuse and/or glycogen storage disease (type 1) (GSD). About 10% of inflammatory HCAs have mutations involving the β-catenin gene [10,11].

Pathogenesis is the result of mutations leading to altered or overexpressed glycoprotein 130 which activates the JAK-STAT3 pathway, leading to increased levels of acute phase reactants and this, in turn, allows inflammatory cell infiltration into the adenoma [12].

Patients present with "systemic inflammatory syndrome" characterized by fever, leukocytosis, and elevated serum CRP levels. These lesions are associated with increased risk of bleeding (> 30%) and a risk of malignant transformation (5–10%) [13,14].

Pathological hallmark includes sinusoidal prominence, infiltration of polymorphous inflammatory cells, scattered areas of peliosis, tortuous and thickened arteries, and diffuse ductal reaction. Lipid within these types of nodule can be occasionally seen; however, it is less

Table 1
Molecular and pathologic classification of hepatocellular adenoma.

	Inflammatory	HNF-1 α-mutated	β-Catenin-mutated	Unclassified
Incidence	40–50%	30–35%	10–15%	10%
Risk factors	Obesity, alcohol	HNF1A germline	Androgen, liver vascular disease	–
Clinical presentation	Systemic inflammatory syndrome, Raised GGT and alkaline phosphatase, older patients.	Liver adenomatosis, female predisposition	Malignant transformation, male predisposition, younger patient	–
Influence of oral contraceptive	+ + +	+ +	+	+ +
Characteristic Imaging findings	Intermediate T2W signal intensity, "Atoll sign" Intense arterial enhancement that persists on venous and equilibrium phases	Loss of signal intensity on opposed-phase images (due to microscopic fat)	Vaguely defined T2W hyperintense scar, Ill-defined areas of T2-weighted hyperintensity, lack of intracellular fat	No typical MR characteristics
Malignant transformation	+/+ + for beta-catenin positive inflammatory adenomas	+	+ + +	+
Molecular signature	IL6ST, STAT3, FRK, GNAS, JAK1 mutations CTNNB1 exon 7/8: 4%, exon 3: 6%	HNF1Amutation	CTNNB1mutation exon 7/8: 3%, exon 3: 7%	No mutation No mRNAs
Glutamine synthetase	Negative/focal positive	Negative	Positive (weak/diffuse)	Negative
C-Reactive protein	Positive	Negative	Negative	Negative
Serum amyloid A	Positive	Negative	Negative	Negative
Histology	- Inflammatory infiltrates - Sinusoidal dilatation - Dystrophic arteries	- Tumor steatosis - Microadenoma - Less hemorrhage	- Cytological atypia - Cholestasis - Size > 5 cm	No association
Liver fatty acid-binding protein	Positive	Negative	Positive	Positive

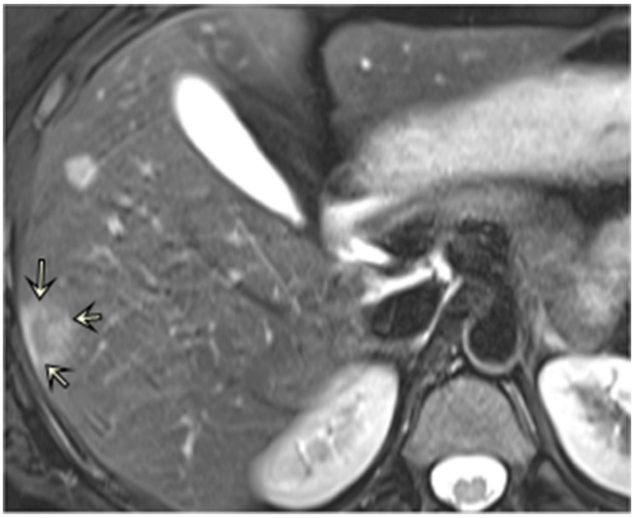

Fig. 1. 34-year-old women with hepatic adenoma. The lesion shows peripheral rim hyperintensity with isointense center relative to liver on T2-weighted image (A) (arrow), "atoll sign" a characteristic sign of inflammatory subtype.

widespread compared with HNF-1α HCA.

A subset of atypical focal nodular hyperplasia with prominent telangiectasias or sinusoidal dilatation (telangiectatic focal nodular hyperplasia), characterized by the absence of nodular architecture and by its mild architectural distortion, is now recognized as an inflammatory adenoma based on molecular genetics and proteomic profiling.

3.1.1. Imaging findings

MRI demonstrates T2 intermediate or hyperintense signal with a characteristic "*atoll sign*", which shows a peripheral rim of T2 intermediate or hyperintensity with an isointense center (Fig. 1). The appearance of the atoll sign is thought to be due to sinusoidal dilatation within inflammatory HCA [17]. T2 hyperintense peripheral areas may reflect high water content in these blood-filled regions. These areas enhance in the venous phase; whereas, the rest of the tumor enhances in the arterial phase [15].

On gadolinium-enhanced images, inflammatory HCA shows a strong arterial enhancement that may persist on delayed phases, though is not always seen (Fig. 2). Also, inflammatory HCA usually appear hypointense to the background liver parenchyma on the hepatobiliary phase on gadoxetic acid–enhanced MR (Fig. 3). Occasionally, inflammatory HCA may also show hyperintensity on the hepatobiliary phase and thereby mimic the appearance of focal nodular hyperplasia (Fig. 4). This could be the result of reduced blood flow due to large cavities and sinusoidal dilatation in inflammatory HCA [10]. In addition, expression of organic anionic transport protein (OATP1B1 and OATP1B3) plays an important role in hepatobiliary uptake. Therefore, signal intensity in hepatobiliary phase can be related to the level of expression of transporter proteins within each lesion [16]. Glutamine synthetase immunohistochemistry, introduced only recently as a clinical tool, has been shown to increase pathologist accuracy for separating these two entities.

3.2. HNF1α-mutated subtype

Hepatocyte nuclear factor 1 alpha (HNF1α)-mutated is the second most common subtype of adenomas and accounts for 30–35% of all adenomas. This type is exclusively found in women. Ninety percent of these women are taking OCPs. This subtype of adenoma can manifest as multiple lesions in about 50% of cases. Association has been shown with maturity-onset diabetes of the young (MODY) and familial hepatic adenomatosis.

Pathogenesis of this subtype of HCA comprises genetic alterations directly from exogenous estrogens resulting, leading to a nonfunctional HNF-1α transcription factor, ultimately resulting in intracellular lipid deposition/steatosis due to a complex mechanism involving suppressed gluconeogenesis-activated glycolysis, and promotion of fatty acid biosynthesis. Defective transport of fatty acids and intracellular deposition of fat can be attributed to the decreased fatty acid binding protein-1.

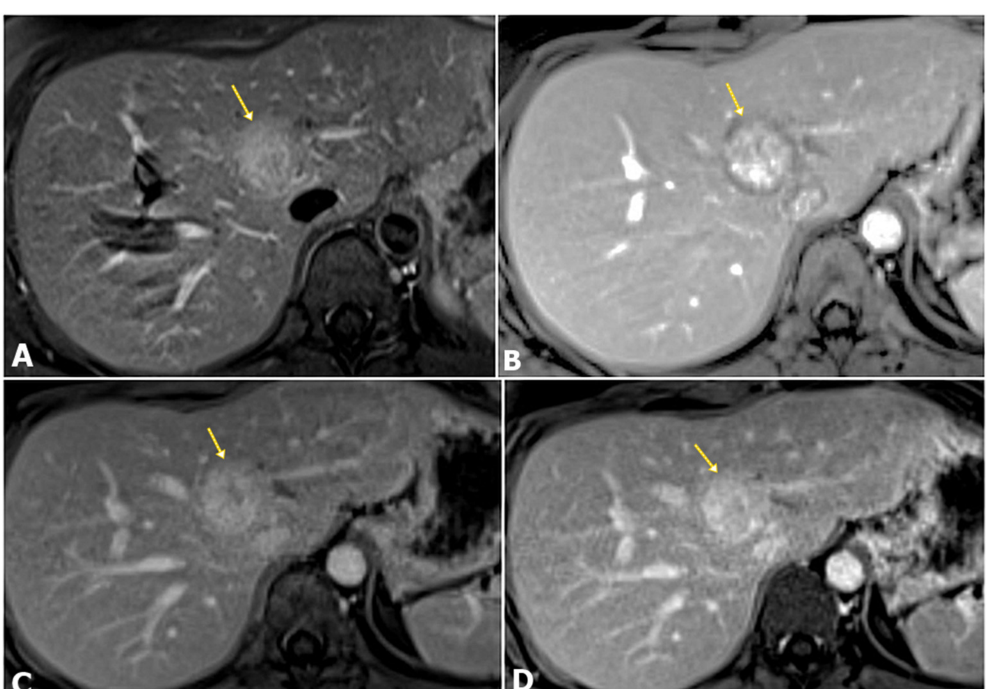

Fig. 2. 45-year-old asymptomatic women with inflammatory hepatic adenoma. Segment 4a mass (arrow) is hyperintense on fat-saturated T2-weighted sequence (A). It shows arterial hyperenhancement (B) that persist on venous (C) and equilibrium phases (D).

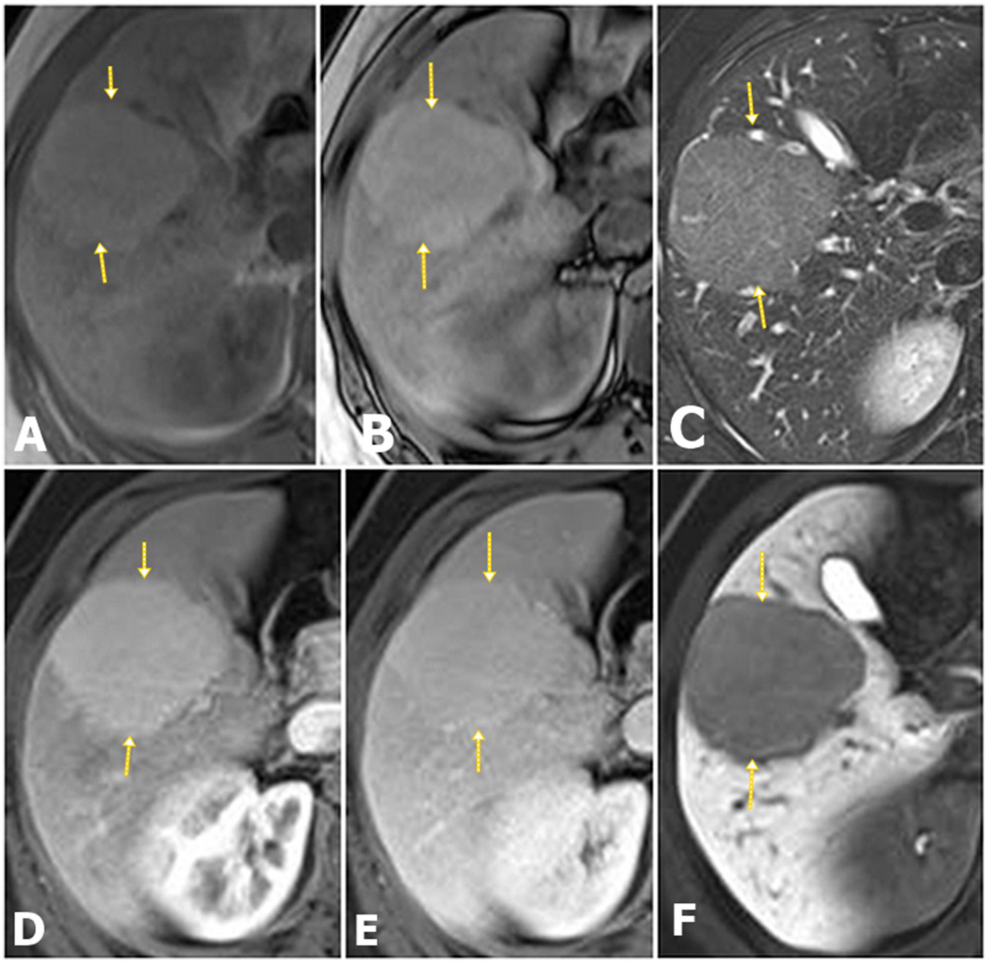

Fig. 3. 61-year old male with typical inflammatory hepatic adenoma (arrows). It appears iso- to slightly hyperintense to liver on T1-weighted image (A) without drop of signal on opposed-phase T1-weighted image (B) and demonstrates T2-weighted hyperintensity (C). There is homogenous arterial phase enhancement (D) that persists into the portovenous phase (E). No uptake is seen on hepatobiliary phase (F) with hepatocyte-specific contrast agents (Gadoxetate disodium).

3.2.1. *Imaging findings*

On MR examination, HNF-1α-mutated subtype of HCA frequently shows microscopic fat deposition as loss of signal intensity on opposed-phase T1-weighted sequences. Significant signal drop in T1 opposed-phased imaging for predictive HNF-1α-mutated HCA is reported to be 85% sensitive and 100% specific, with a 100% positive predictive value and a 94% negative predictive value, respectively [17]. HNF-1α-mutated subtype of HCA shows moderate arterial enhancement that does not persist during the delayed phase (Fig. 5).

3.3. *β-Catenin-mutated subtype*

β-Catenin-mutated subtype is the least common subtype, accounting for 10–15% of all HCAs. This subtype of HCA originates from activating mutations of the catenin β1 gene (CTNNB1), which leads to unrestrained hepatocyte proliferation. β-Catenin has a key role in hepatocyte development, differentiation, proliferation, and regeneration. Mutation of β-catenin itself or mutation of cytoplasmic degradation complex causes sustained activation of β-catenin and excessive nuclear accumulation, which results in autonomous growth of hepatocyte and HCA formation [18]. Avid, diffuse, and homogeneous glutamine synthetase (GS) staining has been shown in β-catenin–mutated HCA.

β-Catenin-mutated adenomas are associated with glycogen storage disease (GSD), familial adenomatous polyposis, and androgen administration [19]. These also have a greater risk of malignant transformation to hepatocellular carcinoma (HCC) [20]. Risk of malignant transformation of HCA to HCC ranges from 4.2% to 13.0% [21]. However, in one study, HCC associated with adenoma was found in 46% of β-catenin-mutated tumors [22].

3.3.1. *Imaging findings*

β-Catenin-mutated adenomas do not have any particularly specific MRI imaging features. They may appear homogeneous or heterogeneous with lack of intracellular fat and demonstrate a vaguely defined T2-hyperintense scar and ill-defined areas of T2-weighted hyperintensity [10]. After administration of intravenous contrast, early hyperenhancement can be seen, which may (or may not) persist on the venous and equilibrium-phases. Some lesions can demonstrate washout, which is non-specific.

Atoll sign is classically described in inflammatory HCA; whereas, scar in β-catenin mutated subtypes [10,23]. Presence of the atoll sign with a scar on imaging may differentiate between β-catenin–positive inflammatory HCA and β-catenin–negative inflammatory HCA [10]. It is essential to identify β-catenin–positive inflammatory HCA whenever possible as there is additional chance of malignant transformation of this subset of β-catenin–positive inflammatory HCA [10].

β-Catenin–mutated HCA may also demonstrate uptake of gadoxetic acid during hepatobiliary phase and mimic focal nodular hyperplasia and pose a diagnostic dilemma [24]. Expression of hepatocyte transporters (OATPB1/B3 and MRP3) have been linked with uptake of gadoxetic acid [25].

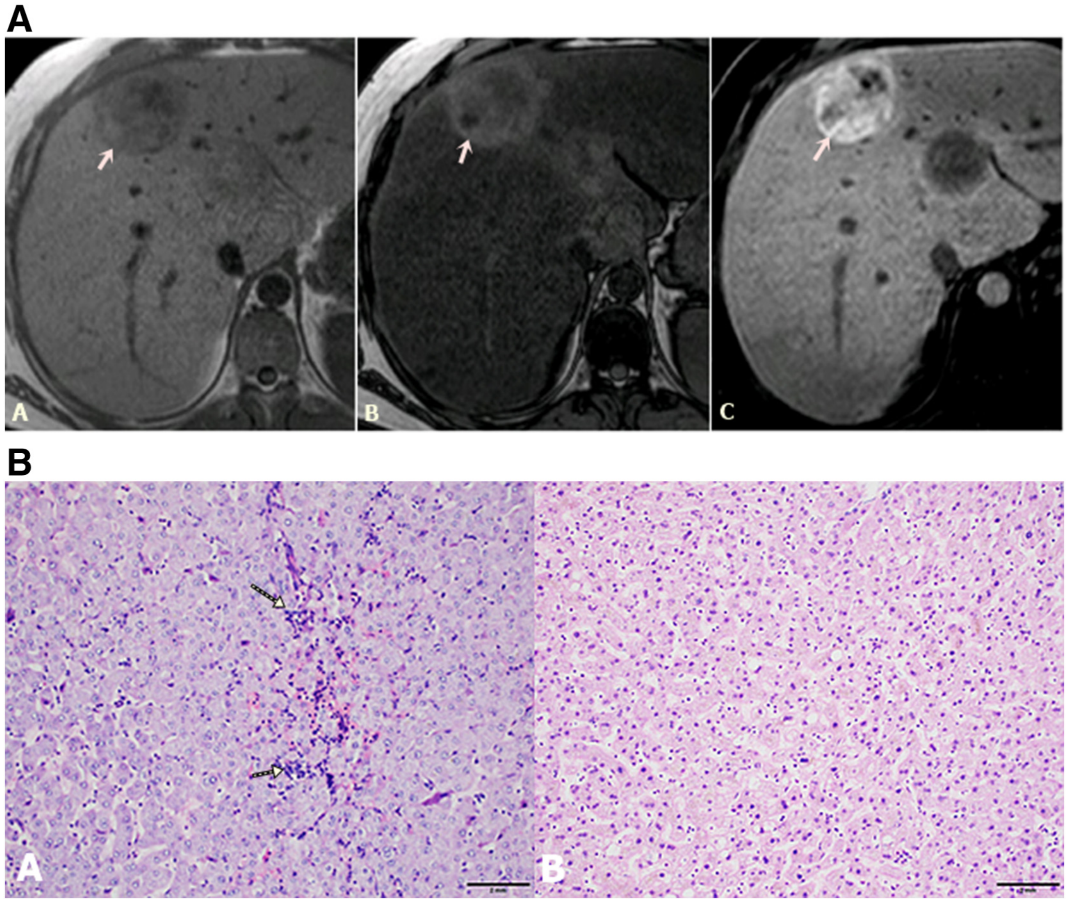

Fig. 4. a. 47 year-old-women with an atypical inflammatory hepatic adenoma (arrow). It shows heterogeneous signal on T1-weighted image reflecting presence of hemorrhage or necrosis. There is diffuse hepatic steatosis on the background, which is seen as diffuse drop of liver signal on opposed-phase T1 image (B). However, it retains contrast in hepatobiliary phase (C) mimicking focal nodular hyperplasia (FNA).
b. A: High power photomicrograph of normal hepatocytes (H and E stain ×20). B: Core biopsy needle in a 38 year-old-women with inflammatory HA. H and E stain (×20) show hepatocytes that are separated by dilated sinusoids (arrows) with foci of inflammation (arrow heads).

3.4. Unclassified subtype

Unclassified subtype accounts for approximately 10% of cases and encompasses all other adenomas, which do not belong to the previously described categories. They are poorly understood but may become malignant.

3.4.1. Imaging findings

No specific MR imaging patterns or other imaging features have yet been proposed to definitively characterize these unclassified HCAs [7].

3.5. Recent developments and expanded system of classification

Recently an additional subtype of HCA has been recognized, called the *sonic hedgehog–activated adenoma*, which accounts for 4% of all HCA and previously considered to be unclassified. Sonic hedgehog–activated hepatocellular adenomas show a fusion of the inhibin-Beta E Subunit (INHBE) and GLI1 genes [20,26]. Sonic hedgehog genetic pathway activated adenoma has a higher propensity to bleed (Fig. 6), and therefore remain clinically important [26].

Additionally, a group of heterogenous adenomas has demonstrated a high propensity for developing malignant transformation. This group includes *androgen-associated adenomas*, *pigmented adenomas*, and *myxoid adenomas*. The pigmented adenomas are characterized by the presence of heavy lipofuscin deposition; whereas, myxoid adenomas are characterized by abundant myxoid material dissecting through the tumors [27,28]. Further, it has been suggested that beta-catenin–activation and pigmentation could be secondary to events along the pathway to malignant transformation of any histologic subtype [28].

These descriptions do not fit well into the existing schema of classification. Therefore, an expanded system for classifying hepatic adenomas has been proposed based on *identifiable risk factors* such as exposure to estrogen, androgens, glycogen storage disease versus no identifiable risk factors [28]. Based on this classification, estrogen-induced adenomas include HNF-1α mutated (40%), inflammatory (50%), and unclassified (10%) adenomas (Table 2). Myxoid type of adenomas has been described as Protein Kinase A–Associated adenomas in this classification, and exclusively consists of HNF-1α mutated variety. Beta-catenin–activation and pigmentation can be seen with any of these subtypes and may represent a risk factor for malignant transformation.

HCA is often treated conservatively; however, surgical intervention is preferred in larger lesions (> 5 cm) due to an expected higher risk of malignant transformation. Surveillance MRI after 6 months of cessation of OCPs can decide the next step of management. Regression in size of HCA may indicate a non-aggressive subtype (Fig. 7). Follow-up should be performed, initially every 6 months, and if the lesion shows no further alteration, follow-up can be stopped or repeated yearly until menopause. Adenoma gradually increasing in size on surveillance imaging may indicate malignant transformation (Fig. 8).

Lesions > 5 cm in size or β-catenin-mutated adenomas with additional risk factors such as male sex, steroid use, glycogen storage disease or underlying viral hepatitis, a surgical treatment is clearly recommended. Recently, other management options including minimally invasive techniques like radiofrequency ablation (RFA) and

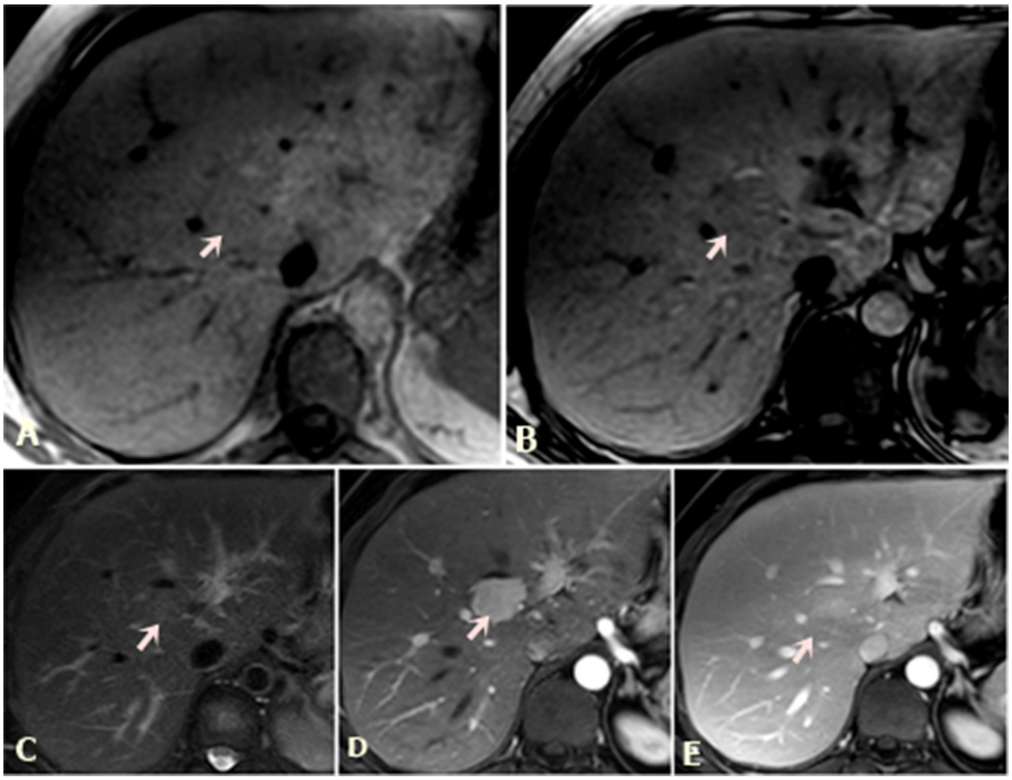

Fig. 5. 27 year-old-women has HNF-1 α-mutated hepatic adenoma (arrow). The mass appears isointense to liver on T1WI (A) with drop of signal on opposed-phase T1WI (B) reflecting presence of microscopic fat. It demonstrates iso to intermediate signal intensity on T2W sequence (C). Contrast enhanced image show arterial phase enhancement (D), however, it appears iso to liver on equilibrium phase (arrow on E).

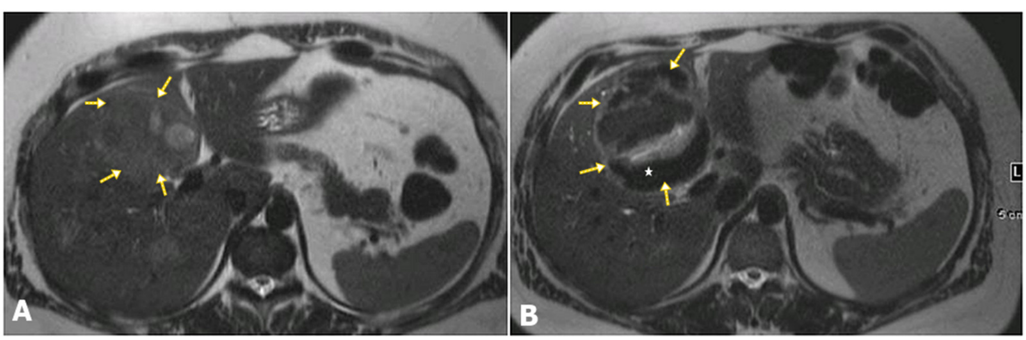

Fig. 6. 40-year-old women with HA complicated by hemorrhage. The left liver lobe HA appear homogenously hyperintense to liver on T2WI (arrow on A). One year later, same lesion has significantly increased in size and appears heterogeneous with hypointense areas to liver reflecting hemorrhage (B).

Table 2
Expanded classification of hepatocellular adenoma.

	HNF1-alpha inactivated	Inflammatory adenomas	Unclassified adenomas
Estrogen-related adenomas	40%	50%	10%
Androgen-related adenomas	10%	20%	70%
Glycogen storage disease adenomas	–	70%	30%
Adenomas with no identifiable risk	20%	20%	60%
Protein kinase A–associated adenoma	100%	–	–

transcatheter arterial embolization (TAE) are advocated [29].

Management guidelines of HCA are discussed in the flowchart (Fig. 9).

3.6. Adenomatosis

Adenomatosis is a term coined by Flejou et al. in 1985 [30]. It is a distinct entity and is defined as presence of multiple (> 10) HCAs without known risk factors, such as history of steroid use, OCP intake or underlying GSD. Absence or occlusion of portal vein or presence of portohepatic venous shunts is seen in these patients [31]. Patient taking OCPs and presenting with multiple adenomas should not be classified as having “adenomatosis”.

4. Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is the 2nd most frequent benign hepatic neoplasm. FNH is a hyperplastic response to a localized vascular abnormality. It can be considered as a benign congenital hamartomatous malformation.

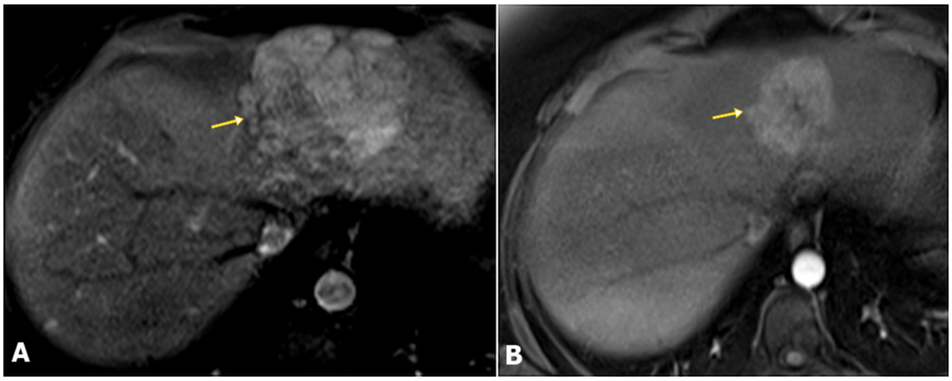

Fig. 7. 28-year-old female with known hepatic adenoma, follow up after cessation of OCP. (A) T1-weighted GRE arterial phase image shows a 7.5 cm lesion (arrow) with heterogeneous arterial enhancement. The lesion is isointense in the venous and equilibrium phases (not shown). Biopsy revealed adenoma. (B) T1-weighted GRE arterial phase image obtained six months after stopping OCP use shows reduction of the adenoma to 5 cm (arrow).

FNH is mostly seen in the same group of patients as HCA, especially with history of OCP consumption. However, association of FNH and OCPs remains controversial. In a 9-year study of 216 women, Mathieu et al. suggested that neither the size nor the number of lesions is influenced by OCP use [32]. Unlike in HCA, discontinuation of OCPs will not lead to a reduction in size or number of FNH, based upon their results.

In 2008, the WHO expert working group stated that women with FNH could continue to use hormonal contraception, as the advantages to use outweigh any potential (yet to be established) risks.

FNH with sinusoidal dilatation and FNH with cytological atypia are two subtypes of FNH. On pathology FNHs > 5 cm in diameter often show a central scar composed of fibrous connective tissue, cholangiocellular proliferation, and vascular deformity. Hemorrhage and necrosis occur within the lesion, unlike HCA. No malignant degeneration has been observed [14,33]. As mentioned earlier, telangiectatic focal nodular hyperplasia (FNH) is now recognized as an inflammatory adenoma.

4.1. *Imaging findings*

On MR imaging, classic FNH appears as isointense lesion on T2-weighted images and iso to slightly hypointense on T1-weighted images. On contrast-enhanced sequences, they show homogeneous arterial enhancement compared to background liver parenchyma. FNH appears isointense (apart from the scar) to the liver parenchyma during the equilibrium phase. A characteristic scar, when present, appears as a hyperintense stellate area on T2-weighted images and is hypointense on fat saturated T1-weighted images during the arterial and portal-venous phases, but which demonstrates slight or gradual hyperintensity during the equilibrium phase (Fig. 10).

After Gd-BOPTA and Gd-EOB-DTPA administration, FNH is isointense or slightly hyperintense to the surrounding liver parenchyma on delayed and hepatobiliary phase [34].

This unique feature differentiates them from HCAs, which display hypointensity of the solid, non-hemorrhagic components of the lesions (apart from the inflammatory subtype). The diagnostic accuracy of gadoxetic acid–enhanced MR imaging to differentiate HCA vs. FNH is presumed high but given the heterogenous behavior of the inflammatory subtype of FNH, it might be overestimated, and the topic needs further supporting studies [35–37].

Heterogeneity and hyperintensity on T1-weighted images, lack of central scar, strong hyperintensity on T2-weighted images, and persistent contrast enhancement on delayed images have been described with telangiectatic focal nodular hyperplasia, which is now described as a variant of inflammatory HCA [38].

Table 3 shows the differences between hepatocellular adenoma and focal nodular hyperplasia.

5. Hemangioma

Liver hemangiomas are the most common benign liver lesions. On cut section they show large, well-defined blood-filled spaces lined by a single layer of endothelium and separated by fibrous septae [39]. They are usually found incidentally on imaging and are often asymptomatic [40].

The natural history of hepatic hemangiomas is not well understood. A study by Conter et al. showed use of OCPs could lead to enlargement of pre-existing hemangiomas or recurrence after resection, although this is controversial. However, there is no published data to support that OCPs cause formation of hemangiomas [41]. A case-control study by Gemer et al., of 40 women with hemangiomas and 109 controls concluded that liver hemangiomas were not associated with use of OCPs or influenced by menstrual or reproductive hormones [42]. Therefore currently, there is no clear association between OCPs and hepatic hemangioma formation.

6. Hamartomas

In 1974, O'Sullivan et al. described three cases of liver hamartomas in patients on OCPs, but later thought them more likely to represent adenomas [43]. The following year, in 1975, Christopherson et al. described three cases of liver hamartomas while evaluating hepatic tumors in women on OCPs [44]. Goldfarb et al. performed a literature review in 1976 regarding the association of OCP use with benign hepatic neoplasia, but found a lack of consistency in histologic criteria for diagnosis [45]. All case reports of liver hamartomas in patients on OCPs have been dated back to timeworn literature and are not currently considered to have causative association.

7. Hepatocellular carcinoma (HCC)

Ninety percent of primary liver cancers are hepatocellular carcinomas. The main risk factors for developing primary liver cancer include chronic infection with hepatitis B or C virus, alcohol consumption, and exposure to aflatoxin B1 [46]. The risk of developing HCC in women taking OCPs is very low and remains speculative.

In 2015 Ning An performed a dose–response meta-analysis of observational studies to quantitatively summarize the existing evidence regarding association between OCPs and liver cancer. It summarized the evidence of fourteen case–control and 3 cohort studies and concluded that OCP use does not have a significant positive effect on the risk of liver cancer [46]. Similarly, Waetjen et al. study showed no support for a measurable effect of OCPs in primary HCC based on data from the USA, Sweden, and Japan.

An Armed Forces Institute of Pathology review of 128 cases of HCC by Goodman et al. reported no convincing association of HCC development in women with history of OCP use [47]. Conversely, a study by Yu et al. demonstrated that use of OCPs for > 5 years was linked to an

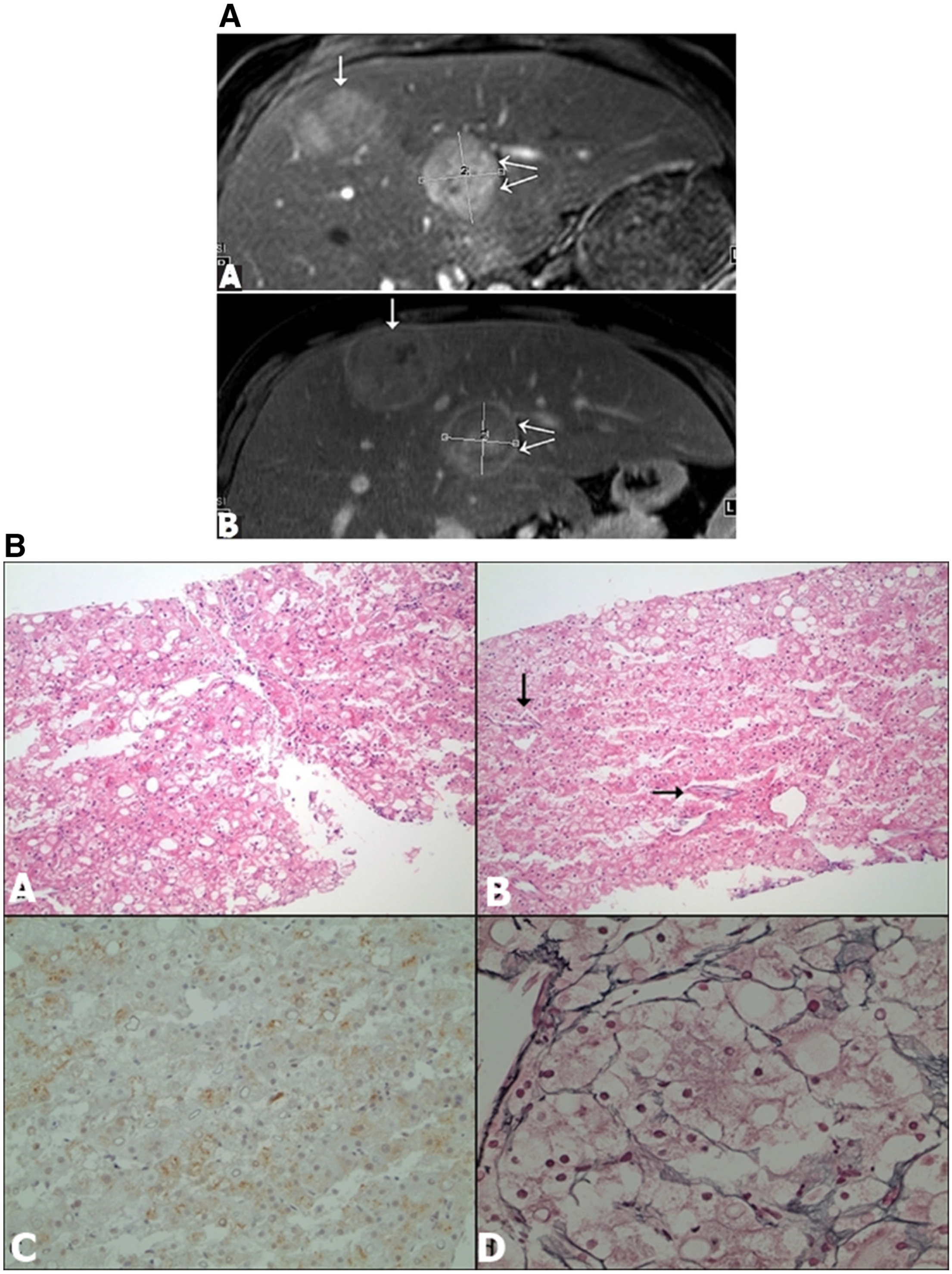

Fig. 8. a: 31-year-old man with known glycogen storage disease Type-1a undergoing surveillance liver imaging for known adenomas. Index images of two hepatic lesions with an interval of 6 months. (A) Fat-suppressed T1W fat post-contrast image acquired in Nov 2014. (B) Fat-suppressed T1W fat post-contrast image obtained in May 2014. The anterior lesion (single arrow) shows interval decrease in size on follow-up imaging; whereas, the posterior lesion (double arrows) is slightly increased in size. Biopsy was performed based on this finding (see next slide).

b: (A) In low-power magnification (hematoxylin and eosin stain), there is moderate steatosis with many ballooned cells, some containing Mallory–Denk bodies. (B) In low-power magnification (hematoxylin and eosin stain), there are increased unpaired arteries (arrows). (C) In low-power magnification, there is focal Glypican-3 staining of the tumor cells. (D) In higher magnification, a reticulin stain shows focal loss of the reticulin framework. Findings are diagnostic of and diagnosis of malignant transformation was confirmed.

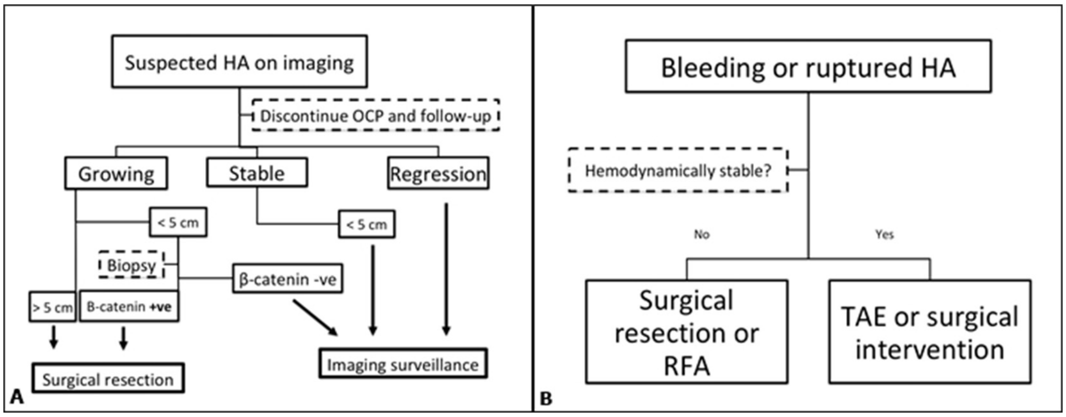

Fig. 9. Algorithm for the management guidelines of HA. (HA: hepatic adenoma, RFA: radio frequency ablation, TA: trans arterial embolization).

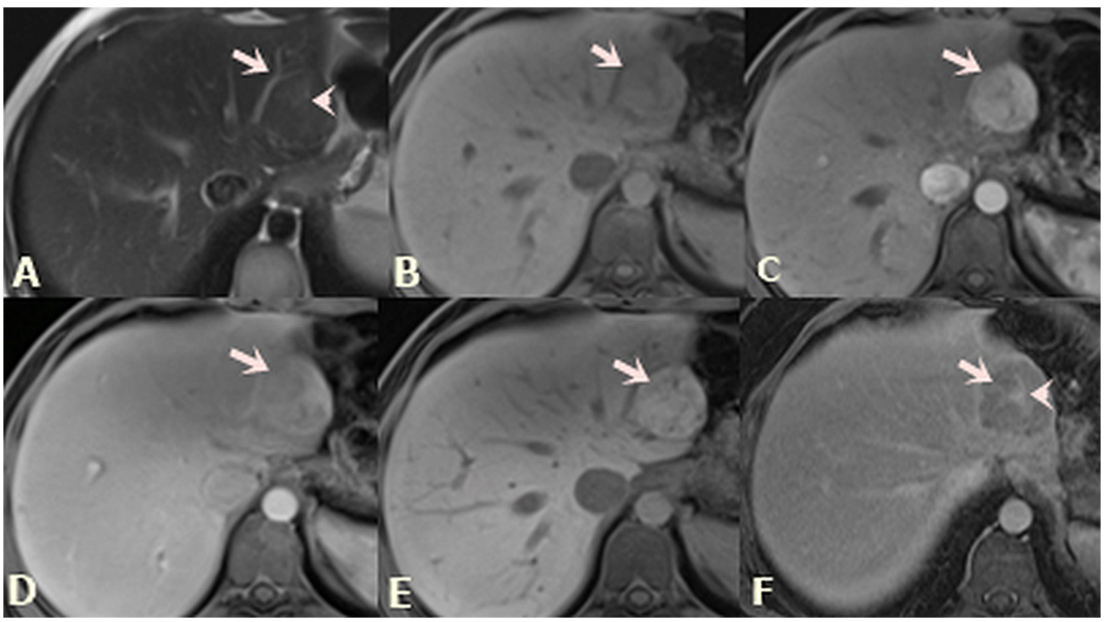

Fig. 10. 29 year-old-women on OCPs had focal liver lesion consistent with FNH (arrow). Left liver lobe mass appears isointense to liver on T2 (A) and T1-weighted images (B). Note slightly hyperintense central scar on T2W image (arrowhead) (A). Post contrast images with hepatic-specific contrast, the lesion show arterial phase enhancement (C), and appear isointense to liver on venous phase (D) and retains contrast on delayed hepatobiliary phase (E). The central scar appears hypointense on precontract T1W (B) and post contrast images (C–D). However, it shows enhancement (arrowhead) on a follow up Gadobenate Dimeglumine MR performed 6 months later.

increased risk of HCC in women, independent of seropositive viral hepatitis status. Given discrepant results in the literature as described above, more research in this area may be warranted in the future.

Other studies have shown that the salient features of HCC in patients using OCPs are different, in that the HCC usually develops in a non-cirrhotic liver, does not infiltrate surrounding tissues and rarely metastasizes [48]. Patients often present with fewer symptoms and lower alpha-fetoprotein levels; however, they also commonly present with hemoperitoneum due to increased vascularity and intraperitoneal rupture [48]. Survival rate is usually higher in these patients.

8. Budd-Chiari syndrome and venous thrombosis

Budd-Chiari syndrome (BCS) is defined as obstructed hepatic venous outflow due to occlusion of the hepatic veins or inferior vena cava. In western societies, BCS is caused mainly by thrombosis of hepatic veins.

OCPs have been linked with an increased incidence of hepatic vein thrombosis (Budd-Chiari syndrome) as well as portal vein thrombosis. It often occurs with an underlying hypercoagulable state including myeloproliferative disorder, acquired abnormalities of coagulation such as lupus or anti-cardiolipin antibodies, as well as due to inherited abnormalities including protein C and S deficiency or abnormalities of clotting factors V and II [49,50]. In addition, BCS has also been implicated in the development of HCA [28].

A study by Valla et al. indicated that the risk of hepatic thrombosis significantly increases in women having recently used oral contraceptives as compared with non-users [51]. Hepatic venous thrombosis could be sequela of drug-induced hepatocellular injury and genetic predisposition.

BCS could be classified as fulminant (few days), acute (≈1 month), subacute (≈3 months) and chronic syndromes. Fulminant and acute forms present with diffuse hepatic necrosis, whereas subacute form manifests with minimal necrosis. Chronic form presents with development of portal hypertension and congestive cirrhosis [52]. Primary BCS is linked with venous lesions (phlebitis, thrombosis or fibrosis) [53]. On the other hand, veno-occlusive disease has classically been identified a separate entity but causes similar physiological changes and hepatic

Table 3
Focal nodular hyperplasia vs. hepatocellular adenoma.

	Focal nodular hyperplasia	Hepatocellular adenoma
Occurrence	2nd most common benign hepatic tumor	3rd most common benign hepatic tumor
Pathology	Hyperplastic response to a localized vascular abnormality	Heterogeneous set of genetically disparate tumors with different genetic abnormalities
Epidemiology	Female predominance (M:F = 1:8), commonly seen in 3rd–4th decades of life.	Women of childbearing age group, strongly linked to OCP consumption
Multiplicity	10–20%	20–30%
Clinical features	Generally asymptomatic, normal liver function test	Pain, altered liver function test
Histology	- Fibrous septa and cellular areas of hepatic proliferation - Central fibrous scar which consists of fibrous connective tissue, cholangiocellular proliferation, and malformed vessels - Hemorrhage and necrosis are exceptional within the lesion	- Inflammatory infiltrates - Sinusoidal dilatation - Dystrophic arteries - Tumor steatosis - Microadenoma - Less intralesional hemorrhage - Cytological atypia - Cholestasis - Hemorrhage outside the lesion into liver parenchyma
Malignant transformation	No malignant transformation	Associated with malignant transformation
T1W	Isointense on T1W images, no microscopic fat	Signal drop on T1-opposed phase (microscopic fat), especially in HNF-1 α-Mutated subtype
T2W	Isointense to slightly hypointense	Intermediate to hyperintense
T1W Gd post contrast: - Arterial - Venous - Delayed/equilibrium	- Homogeneous arterial enhancement - Isointense on equilibrium phase	Strong arterial enhancement that persist on delayed phase
Hepatobiliary phase post Gd-EOB-DTPA	Isointense or slightly hyperintense to the background liver parenchyma	Hypointense to the background liver parenchyma

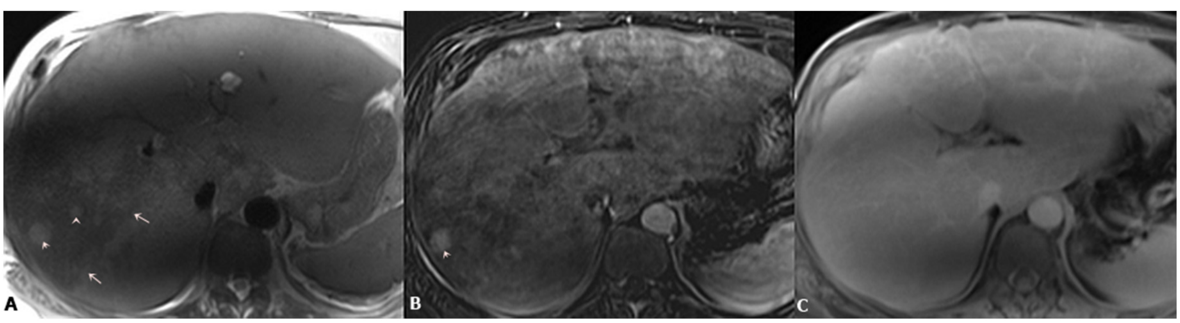

Fig. 11. 43-year-old-women with Budd-Chiari syndrome. The liver demonstrates inhomogeneous T2W signal intensity (A) and diffuse enlargement. There is caudate lobe hypertrophy. Straight demarcation between normal and abnormal liver parenchyma (arrows) (A) indicates underlying perfusional abnormality. Scattered regenerative nodules (arrowheads) are seen (A–B), which demonstrate hyperenhancement during arterial phase (B) and appear isointense to liver parenchyma on equilibrium phase (C).

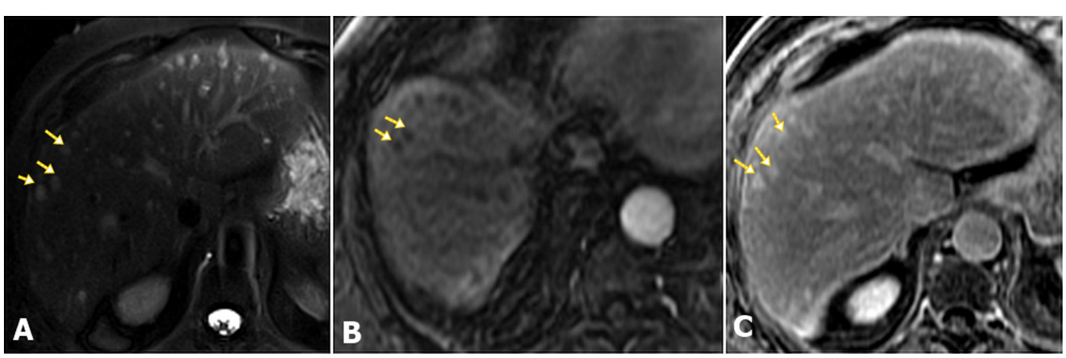

Fig. 12. 51-year-old asymptomatic male with peliosis hepatis (arrows). Multiple peripherally situated tiny hyperintense nodules on T2WI (A) that appear hypointense to liver on arterial phase (B) and demonstrate fill-in enhancement on later post-contrast phases.

outflow blockage. It often occurs due to endothelial injury caused by toxins and leads to microvascular occlusion masquerading most clinical and laboratory findings of primary BCS [53].

8.1. Imaging findings

Imaging may identify presence of IVC or hepatic venous thrombosis in acute phase. After intravenous contrast administration, the liver parenchyma demonstrates early central and delayed peripheral enhancement (flip-flop pattern). MRI findings may vary and demonstrate hepatomegaly, inhomogeneous parenchymal signal intensity, caudate lobe enlargement, regenerative nodules and ascites (Fig. 11). Chronic BCS presents with atrophic veins as well as intraparenchymal venous collaterals [52].

9. Dilated sinusoids and peliosis hepatis

The first report of generalized peliosis hepatis as a complication of long-term use of oral contraceptives was made by Van Erpecum et al. in 1988 [54]. Peliosis hepatis is a rare, acquired vascular disorder characterized by randomly distributed blood cysts communicating with hepatic sinusoids. The pathogenesis of peliosis hepatis is unclear but possibly includes hepatocellular necrosis and injury to the sinusoidal endothelium [55].

However, oral contraceptives do not cause sinusoidal endothelial cell injury, in contrast to other agents such as azathioprine, 6-thioguanine and oxaliplatin. Hence, the mechanism by which oral contraceptives lead to peliosis hepatis remains uncertain. The lesions show regression after interruption of usage with incomplete response, in some cases progressing to cirrhosis [54].

On gross inspection, the liver has a Swiss cheese pattern with multiple blood-filled cystic spaces. Two pathological types have been described:

- The parenchymal type is characterized by hemorrhagic parenchymal necrosis with blood cavities neither lined by sinusoids/fibrosis.
- The phlebectatic type is based on aneurysmal dilatation of central vein with cavities lined by endothelium and fibrosis [56].

Peliosis secondary to OCP use shows profound sinusoidal dilatation with venous lakes [57]. The varied clinical manifestations range from incidental to abnormality in liver enzymes, massive hepatomegaly, liver failure, and life threatening hemoperitoneum [58–60].

Chronic use of OCPs has been associated with sinusoidal dilatation, as seen on liver biopsies. Cessation of OCPs has been shown to regress the severity of peliosis. Patients may present with abdominal pain due to hepatomegaly. Hepatic arteriography shows stretched and attenuated branches of the hepatic arteries with a patchy parenchymal pattern of enhancement.

9.1. *Imaging findings*

The radiological presentation can be focal to diffuse with varying appearances depending on the size and presence of hemorrhage [61]. On MRI, the lesions have low signal intensity on T1-weighted images and hyperintensity on T2-weighted images [63,62]. There is delayed and slow but intense enhancement on contrast-enhanced T1-weighted images (Fig. 12). They are predominately hypointense on hepatobiliary phase with some lesions retaining contrast, indicative of cholestasis [63]. On angiography, lesions show contrast accumulation on the late arterial phase which persists in the portal venous phase [62].

10. Summary

Use of OCPs is associated with an increased risk of certain liver diseases and neoplasms. Recognizing these entities and understanding the potential influence of OCPs is important for successful diagnosis and management. Certain hepatic tumors such as hepatocellular adenoma and tumor-like lesions including peliosis hepatis have a proven association with long-term use of OCPs. Increased incidence of hepatic vein and portal vein thrombosis are often linked with an underlying hypercoagulable state. Association of FNH, hepatocellular carcinoma, hemangiomas and hamartomas with OCPs has randomly been described in the literature but is not clearly established. Further research is needed, particularly with lower dose OCPs, to determine their ultimate effect on patient health.

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