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REVIEW

Hepatic disorders associated with exogenous sex steroids: MR imaging findings

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Abstract

Objective To describe the MRI findings of the effects of exogenous sex steroids on the liver.

Findings Estrogens, progesterone and synthetic testosterone are exogenous sex steroids that may result in a variety of liver diseases, including tumour formation and vascular disorders. These hormones are mainly administered in the form of the oral contraceptive pill (OCP) and anabolic steroids. Both are implicated in hepatic adenoma formation. The HNF-1α-mutated and inflammatory adenoma subgroups are more commonly seen in association with the OCP whereas there is an increased incidence of the β-catenin positive subtype with anabolic steroid use. Furthermore, anabolic steroids are associated with hepatocellular carcinoma resulting from malignant transformation of β-catenin positive adenomas. The oral contraceptive pill may also induce vascular disorders within the liver, some of which are related to the prothrombotic effect of the hormones, such as hepatic and portal vein thrombosis. Other hepatic vascular abnormalities resulting from exogenous sex steroids include veno-occlusive disease and peliosis hepatis.

Keywords MRI Liver · Hepatic adenoma · Oral contraceptive pill · Anabolic steroids · Exogenous sex steroids · Hepatic vascular disorders

Introduction

The oral contraceptive pill (OCP) and anabolic steroids are exogenous sex steroids that are associated with hepatic tumours (Table 1) and a variety of hepatic vascular disorders (Table 2). With widespread use of the OCP and with recreational abuse of anabolic steroids, sex hormone-related, hepatic complications are increasingly being detected on imaging studies. Hepatic adenomas are often detected incidentally and are the most frequent tumours to be associated with oral contraceptives. The subtypes of hepatic adenomas are reviewed along with their distinct imaging features and clinical implications such as haemorrhage and malignant transformation. The MRI appearances of anabolic steroid-induced hepatocellular carcinoma and of sex hormone-associated hepatic vascular disorders are also discussed.

Hepatocellular adenomas

Hepatocellular adenomas (HCAs) are a heterogeneous group of tumours characterised by specific genetic features, pathological abnormalities and tumour biology [1]. Before the advent of oral contraceptives, HCAs were regarded as extremely rare neoplasms [2].

In 2010, the World Health Organisation formally endorsed the Bordeaux group classification which divides HCAs into four subgroups according to genotypic findings, phenotypic characteristics and clinical features [3].

The first of the 4 subgroups is the HNF-1α-mutated HCA group (H-HCA), accounting for 35–50% of adenomas. These adenomas are defined by a mutation of the HNF1A gene, which is involved in hepatocyte differentiation. This subtype almost exclusively affects females and the oral contraceptive pill is implicated in more than 90% of cases [4, 5]. Estrogens in the OCP may act as genotoxic agents and may

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Table 1 Imaging features of liver tumours associated with exogenous sex steroids

Tumour	Clinical comments	T1WI	T2	Signal dropout on out-of-phase T1WI	Haemodynamics	Delayed hepatobiliary phase
Adenomas						
HNF-1α subtype (H-HCA)	Occurs mostly in females >90% associated with the oral contraceptive pill	Iso/hyperintense	Hyperintense	Yes, diffuse	Moderate enhancement in the arterial phase	Hypointense
β-Catenin positive subtype (β-HCA)	Occurs mostly in men Associated with anabolic steroid use	Heterogeneous	Heterogeneous	No	Mild to moderate arterial enhancement An intralesional scar may enhance in the late portal venous phase	Isointense or hyperintense
Inflammatory subtype (I-HCA)	Risk factors including oral contraceptive pill, obesity and alcohol	Iso/hyperintense	Hyperintense rim at periphery (atoll sign)	No (but occasionally focal areas of signal drop out)	Marked arterial phase enhancement and persistent enhancement in the portal venous phase	Hypointense (10% iso or hyperintense)
Unclassified HCA	–	–	–	–	–	–
Hepatocellular carcinoma	Associated with anabolic steroids	Hypointense	Hyperintense	–	Arterial phase enhancement	Iso/hyperintense

be responsible for somatic mutations in HNF-1α-mutated HCAs [1] with resultant increased lipogenesis and hepatocellular proliferation [6].

On MRI, the lesions are usually iso- or slightly T1-hyperintense and mildly T2-hyperintense [7]. These lesions contain fat and demonstrate signal drop on the T1-weighted opposed-phase sequences (Fig. 1) [5]. Moderate arterial phase enhancement may be seen [8]. On MRI with hepatocyte-specific contrast, gadoxetic acid (Eovist in the US and Primovist elsewhere—Bayer Pharmaceuticals, Whippany NJ), they are hypointense in the delayed hepatobiliary phase. Suppression of the liver fatty-acid-binding protein occurs leading to intracellular fat deposition [5], accounting for the steatotic appearance on MRI. The homogeneous signal drop on opposed-phase sequences carries a sensitivity as high as 86% for the diagnosis of H-HCA [1]. Some inflammatory adenomas may also demonstrate signal drop however it tends to be more focal and heterogeneous [9]. Background fatty liver is an associated finding [1].

The second subtype, which comprises 15–18% of adenomas are the β-catenin-positive HCAs (β-HCA) which are characterised by the presence of β catenin-activating mutations. These are associated with the use of anabolic steroids and are more frequently seen in men. This subtype has the potential for malignant transformation, with the risk being highest for patients taking anabolic steroids and patients with glycogen storage diseases [2].

On MRI, β-HCAs are often poorly defined. They are heterogeneous on T2-weighted sequences, demonstrate mild to moderate hypervascularity and demonstrate a central scar in 75% cases, which may enhance in the late portal venous phase [7]. On gadoxetic acid-enhanced MRI, the majority are iso- or hyperintense in the hepatobiliary phase due to overexpression of the organic anion transporting polypeptide 1B3 (OATP1B3, also known as OATP8) [5]. OATP1B3 is considered to be the main uptake transporter of gadoxetic acid in hepatocellular nodules which determines the signal intensity in the hepatobiliary phase [5].

The third subtype are the inflammatory adenomas (I-HCA), which make up 40–55% of all HCAs. They are seen predominantly in young women with OCP use [2]. Other risk factors include obesity and alcohol [5]. Most are iso- to slightly hyperintense on T1-weighted sequences and mildly T2 hyperintense. These lesions may demonstrate an atoll sign on T2-weighted sequences with rim-like T2 hyperintensity (Fig. 2), which typically enhances in the late venous phase, possibly corresponding to dilated sinusoids. This is thought to be characteristic of I-HCAs and has been documented in 27–43% of cases [7].

They demonstrate strong arterial phase enhancement and persistent portal venous phase enhancement [5] (Fig. 3). As previously mentioned, steatosis may be present. The signal drop out on opposed-phase sequences is focal rather than

Table 2 Vascular disorders associated with exogenous sex steroids

Vascular disorder	Associated exogenous sex steroid	Site of vessel occlusion	Pertinent imaging features
Budd-Chiari syndrome	Oral contraceptive pill	Any point from small hepatic veins to junction of IVC & right atrium	Congested, enlarged liver (acute) Peripheral atrophy and caudate hypertrophy (chronic) Early central liver enhancement and reduced peripheral enhancement followed by 'flip-flop' pattern with hypo-enhancing central liver & gradual enhancement of the periphery
Peliosis hepatis	Oral contraceptive pill Anabolic steroids	Sinusoids	Multiple lesions with no mass effect Variable signal enhancement depending on size of lesions, presence of thrombus and age of haemorrhage
Portal vein thrombosis	Oral contraceptive pill	Portal vein	Increased enhancement in arterial phase and decreased enhancement in the portal venous phase Cavernous transformation of the portal vein
Veno-occlusive disease	Oral contraceptive pill	Small, post-sinusoidal venules	Heterogeneous signal Decreased & delayed, patchy enhancement No caudate sparing

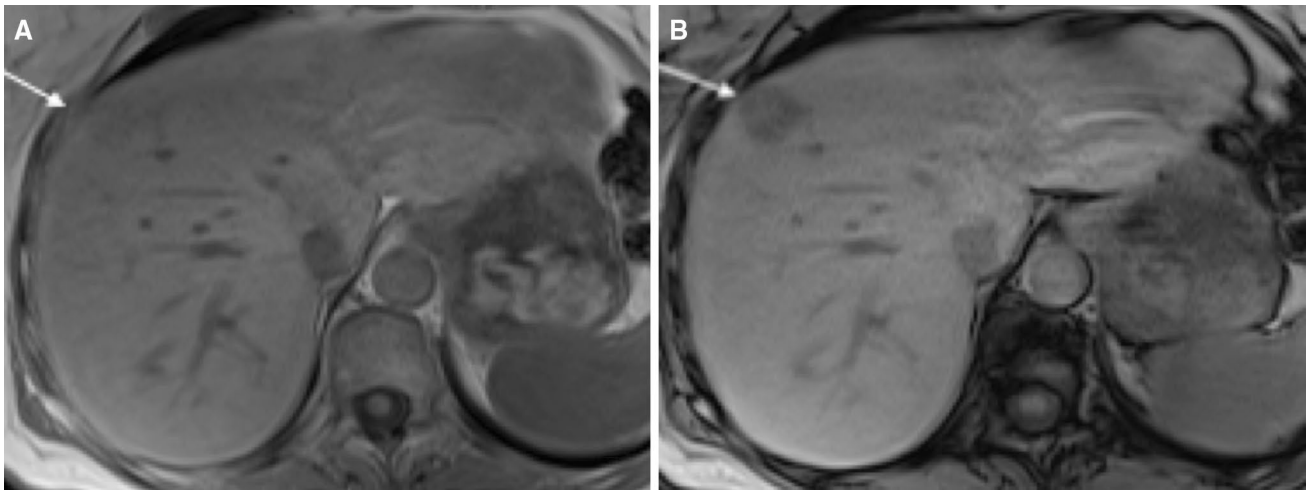

Fig. 1 MRI of the liver in a female with a long history of OCP use with an HNF-1-α mutated adenoma. Axial T1-weighted in phase sequence **a** and T1-weighted opposed phase sequence **b** demonstrate a mildly T1 hypointense lesion in segment 8 of the liver (arrow) with signal drop on the opposed-phase sequences indicating fat content

diffuse and is seen in 38% [2]. Most I-HCAs are hypointense in the hepatobiliary phase (Fig. 3).

I-HCAs carry a higher risk of haemorrhage than other subtypes, which is likely to be related to extensive sinusoids and feeding arteries as well as to the poor connective tissue support [8]. The growth and risk of bleeding of HCAs are influenced by the use of oral contraceptives [10]. Approximately, 10% of I-HCA have β-catenin activation which is considered to promote their malignant transformation. These tend to demonstrate iso- or hyperintensity in the hepatobiliary phase [5].

The fourth subtype accounts for 10% of HCA and has no specific genetic mutations, immunohistochemical nor imaging features.

Hepatic adenomatosis is defined as the presence of greater than ten adenomas involving both lobes of the liver, without a history of steroid therapy or glycogen storage disease. The aetiology is unclear although HNF1A gene mutations and hepatic vascular abnormalities are suggested causes. The condition may involve any subtype of adenoma [1].

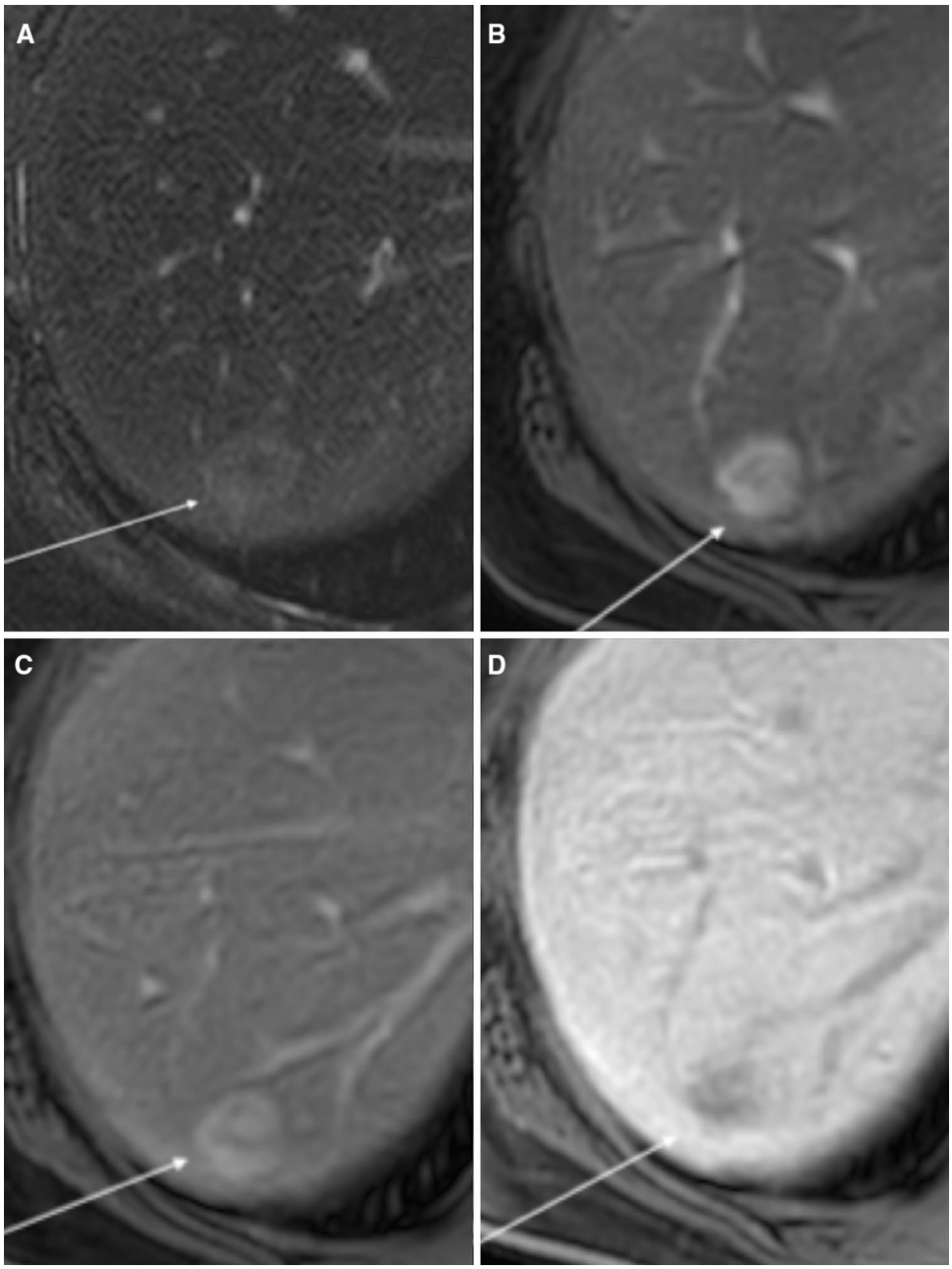

Fig. 2 Gadoxetic acid-enhanced MRI of the liver in a female with a long history of OCP use and an inflammatory adenoma. Axial T2-weighted sequence **a** depicts a T2-hyperintense lesion in segment 7 (arrow) with a peripheral rim of more marked T2 hyperintensity (atoll sign). On the arterial phase-T1-weighted FS sequence **b**, there is moderate arterial phase enhancement. In the portal venous phase **c** there is mild central enhancement and more pronounced enhancement of the rim. In the 20-min delayed hepatobiliary phase **d** the lesion is hypo-enhancing

Hepatocellular carcinoma

Continuous use of anabolic, androgenic steroids in high doses is associated with development of hepatocellular carcinoma (HCC). This occurs amongst athletes and bodybuilders who use anabolic steroids illicitly to rapidly increase muscle mass. The mechanism for carcinoma induction is not well understood, although anabolic steroids are known to induce liver cell proliferation [11]. HCCs following anabolic androgenic steroid abuse is most often encountered in non-cirrhotic livers [12].

The mechanism for carcinogenesis may either be malignant transformation of an adenoma (adenoma carcinoma sequence) or de novo carcinoma. The latter has been described in young patients with Fanconi's anaemia who have been treated with anabolic steroids [13].

Hepatocellular adenoma may undergo malignant transformation to HCC in 3–9%. The β-catenin mutation is an early alteration in the adenoma–carcinoma sequence. HCCs with β-catenin mutations tend to be well differentiated. They tend to result in a significantly lower serum alpha-fetoprotein level and are associated with a relatively

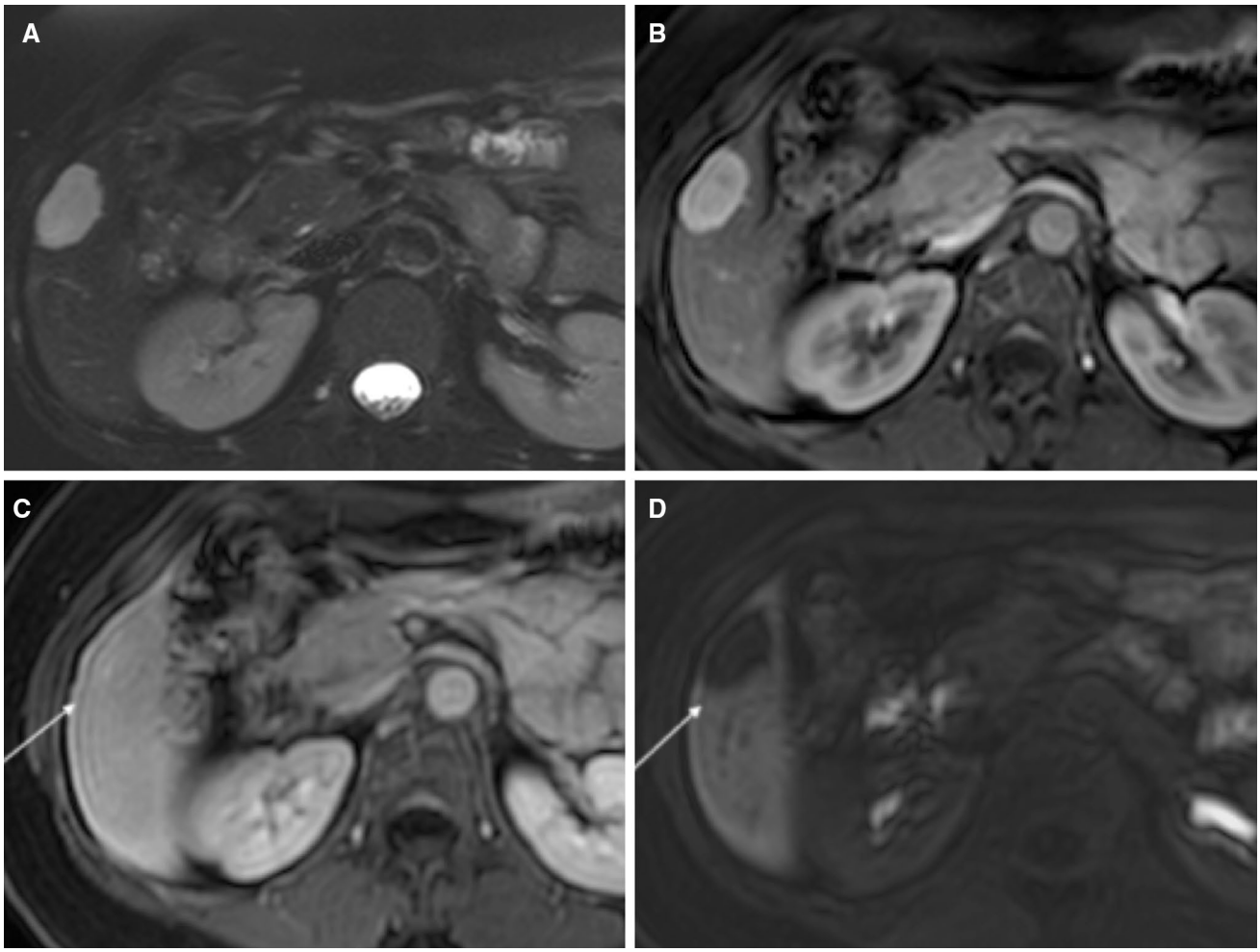

Fig. 3 Gadoxetic acid-enhanced MRI of the liver in a female with a 20 year history of OCP use with an inflammatory adenoma. Axial T2-weighted sequence **a** demonstrates an ovoid T2 hyperintense lesion in segment 5. On the arterial phase T1-weighted FS sequences **b** there is vivid enhancement. Iso-enhancement of the lesion (arrow) is exhibited in the portal venous phase **c** and hypo-enhancement is seen in the 20 min-delayed, hepatobiliary phase **d**

favourable prognosis compared with HCCs without β-catenin mutation [14].

On MRI, β-catenin-mutated HCCs demonstrate T1 hypointensity and T2 hyperintensity, similar to HCCs without the β-catenin mutation. However, they differ from HCCs without the β-catenin mutation as they show higher ADC values and a higher enhancement ratio in the hepatobiliary phase with liver-specific contrast (Fig. 4). The iso- or hyperintensity in the hepatobiliary phase is attributed to a significant positive correlation of expression of β-catenin and OATP1B3 [13]. HCCs that are hyperintense in the hepatobiliary phase may be biologically less aggressive than HCCs that are hypointense in the hepatobiliary phase [15].

Focal nodular hyperplasia

The development of FNH was previously thought to be associated with usage of the oral contraceptive pill, but no known relationship between the oral contraceptive pill and FNH has been established [16]. FNH tends to occur predominantly in women of child-bearing age [17], many of whom are on the oral contraceptive pill. In the past, discontinuing the oral contraceptive pill was recommended in such patients. There is, however, insufficient data to attribute FNH to exogenous estrogen use [18–20]. More recent studies suggest neither the size nor number of FNH lesions are influenced by the oral contraceptive pill [21].

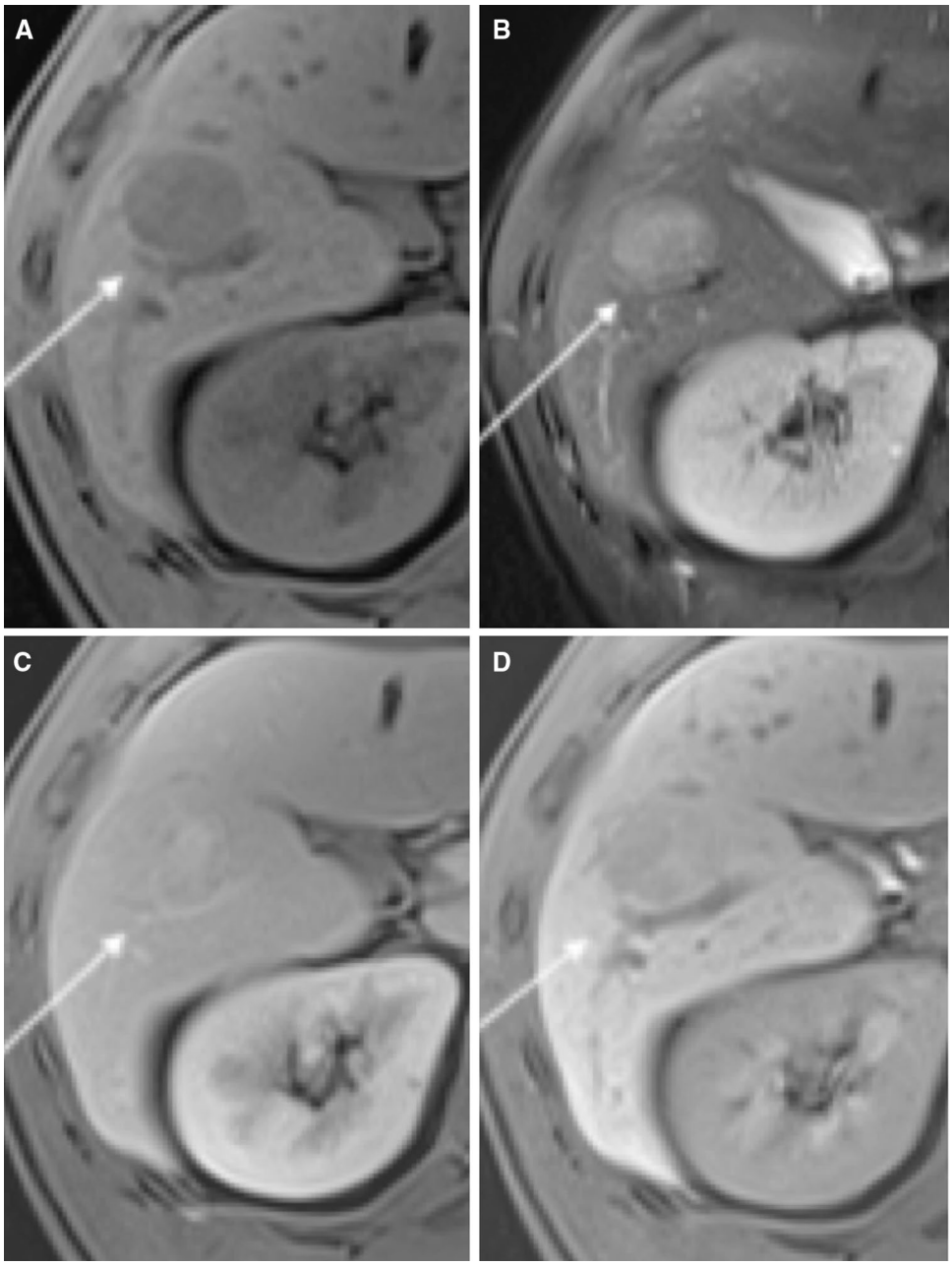

Fig. 4 Gadoxetic acid-enhanced MRI of the liver in a 47-year-old male, bodybuilder with a long history of androgenic anabolic steroid abuse with multifocal β-catenin positive hepatocellular carcinoma. On the axial T1-weighted sequence **a**, a hypointense mass in segment 5/6 is seen (arrow). On the T2-weighted sequence **b** the lesion is mildly hyperintense. In the portal venous phase **c** the lesion exhibits mild heterogeneous enhancement and on the 20-min, delayed, hepatobiliary phase sequence **d** it is heterogeneously iso- to hypoenhancing

Peliosis hepatis

Peliosis hepatis is a rare, benign, vascular lesion characterised by sinusoidal dilatation and formation of multiple blood-filled hepatic spaces [22]. It has been suggested that obstruction of hepatic outflow at the sinusoidal level or hepatocellular necrosis may be pathogenetic mechanisms, however, these are poorly understood [23]. Recognised causes include drugs such as the oral contraceptive pill, corticosteroids and anabolic steroids. In these cases, cessation of the drug results in regression of the lesions [24].

Peliosis hepatis is often asymptomatic, however, correct diagnosis is important as complications include hepatic failure, portal hypertension and liver rupture leading to hemoperitoneum, which, if untreated, is potentially rapidly fatal [25]. In addition, biopsy of these lesions carries a small but well-documented risk of severe haemorrhage [26].

The MRI findings of peliosis hepatis are variable and have only been described in case reports. The signal and enhancement characteristics of the lesions depend on the size of the lesions, presence of thrombus and age of haemorrhage within the cavities [27, 28]. The lesions range in size from 1 mm to several centimetres and typically involve the entire liver, although focal peliosis has been described [25]. The absence of mass effect is thought to be a characteristic finding [23].

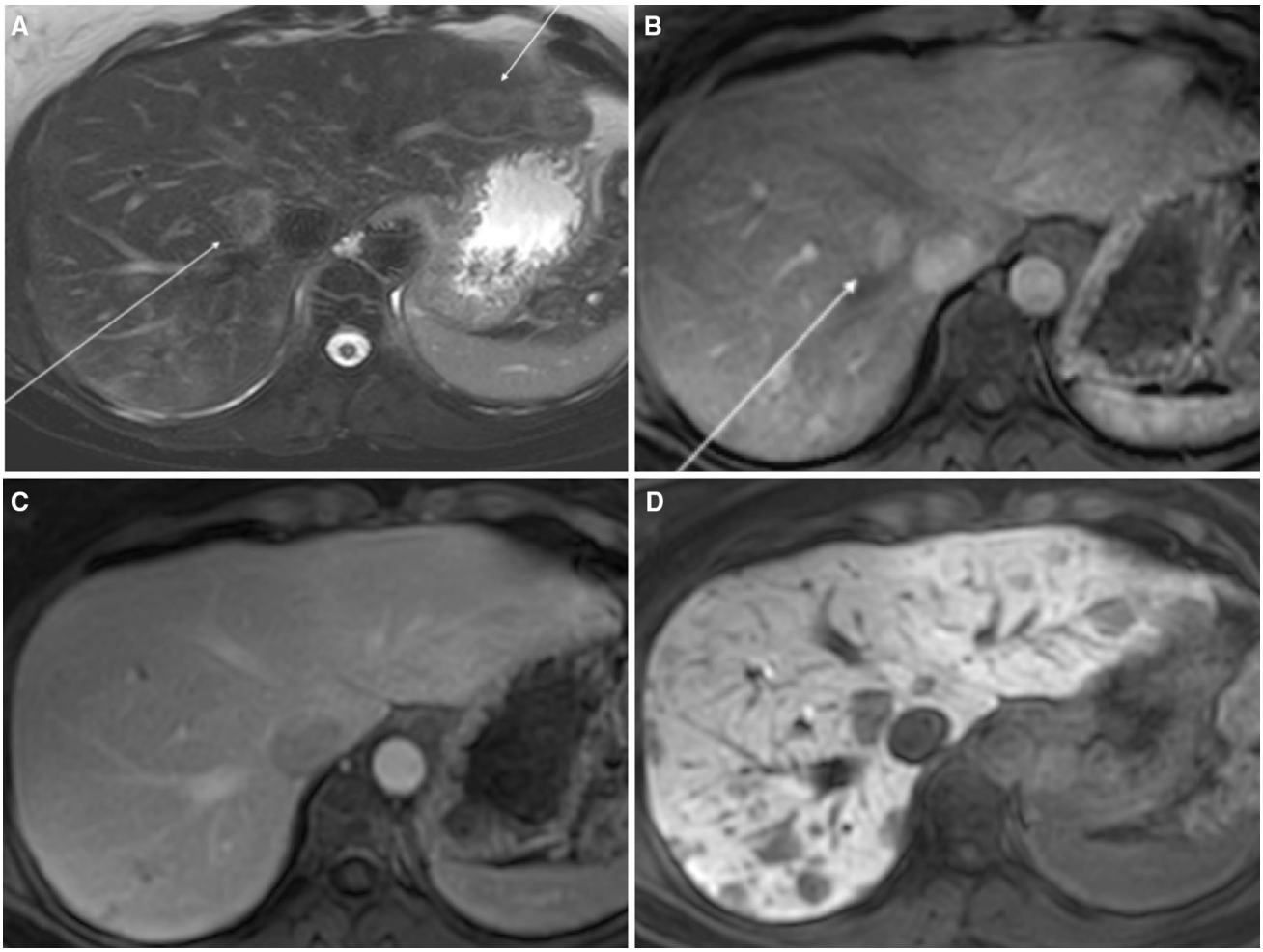

Fig. 5 Gadoxetic acid-enhanced MRI of the liver in a female with a 20-year history of OCP use with biopsy proven peliosis hepatis. On the axial T2-sequence **a** segment 2 and 8 lesions (arrows) are mildly hyperintense. On the T1-weighted FS arterial phase sequence **b** there is moderate enhancement of these lesions and further lesions in segment 7 lesions become more apparent. In the portal venous phase **c** the lesions are isointense with central hypo-intensity. On the 20-min delayed hepatobiliary phase **d**, the lesions are hypo-enhancing and multiple further lesions are seen

On MRI, the T1 signal varies depending on the age of blood products present. Peliosis hepatis lesions tend to be T2-hyperintense (Fig. 5) and there may be central areas of higher T2-signal possibly related to necrosis [22]. On post contrast sequences, several enhancement patterns have been noted. The most often described enhancement pattern is multiple, globular, small areas of central enhancement in the arterial phase (target sign) and centrifugal progression of enhancement in the portal venous phase [26]. This pattern possibly occurs in the early stage of the lesions. A second pattern of hypo-enhancement in the arterial phase followed by progressive enhancement iso or hyperenhancement in the portal venous and delayed phases, resembles a hemangioma [23]. Other patterns of enhancement are highly varied and include centripetal enhancement, an enhancing rim with cystic cavities, a branching appearance due to the vascular component of the lesion [29] and there may be no enhancement at all if the cavities of the lesions are thrombosed [25].

If hepatocyte-specific contrast is used, lesions are predominantly hypo-enhancing, likely related to the paucity of functioning hepatocytes (Fig. 5).

Budd-Chiari syndrome

Budd–Chiari syndrome (BCS) encompasses a heterogeneous group of disorders characterised by hepatic venous outflow obstruction. This may occur at any point from the small hepatic veins to the junction of the IVC and right atrium [30]. In the western hemisphere, the main cause of BCS is hypercoagulative states [31].

Haematological abnormalities, such as myeloproliferative disorders are responsible for the majority of cases, however, many other conditions associated with hypercoagulative diatheses are contributory, including use of the oral contraceptive pill [32]. Oral contraceptives induce production of coagulation factors I, II, VII, IX, X and XII and reduction of antithrombin III concentrations [33].

The incidence of BCS is unknown and is most often seen in women. The clinical presentation and imaging findings depend on the degree and acuteness of venous obstruction as well as the adequacy of the collateral venous outflow [31]. Increased pressure in the hepatic veins results in increased sinusoidal pressure, portal venous stasis and congestion. This may lead to hypoxic damage in adjacent hepatocytes [34]. If the hepatocellular damage is massive, the patient will present with the fulminant form of BCS which is a potentially fatal condition [30]. In such cases, liver failure, ascites and painful hepatomegaly may develop over days to weeks [24].

In an acute presentation of BCS, symptoms develop within weeks. On MRI, there are absent flow voids on T2*-weighted gradient-recalled echo sequences [32] (Fig. 6) with variable signal thrombus in the hepatic veins or inferior vena cava (IVC). Non-enhancement of affected vessels after contrast administration is seen. The liver is globally enlarged due to congestion with areas of decreased T1-signal and heterogeneous areas of increased T2-signal, predominantly in the periphery [31] (Fig. 6). The patency of the caudate vein, which drains separately to the IVC, forms the basis for the enhancement pattern and morphological features of BCS. The postcontrast sequences demonstrate differential enhancement between central and peripheral liver. Early enhancement of the caudate lobe, central liver and around the IVC is observed (Fig. 6). There is decreased peripheral enhancement in the arterial phase due to portal and sinusoidal stasis [24]. The increased enhancement is seen in the areas where venous drainage is less affected such as the caudate lobe [31] (Fig. 7). In the portal venous phase, a "flip-flop" pattern of enhancement is present: there is hypoenhancement of the central liver because of the contrast washout, whereas the enhancement in the peripheral liver gradually increases with accumulation of contrast material [24].

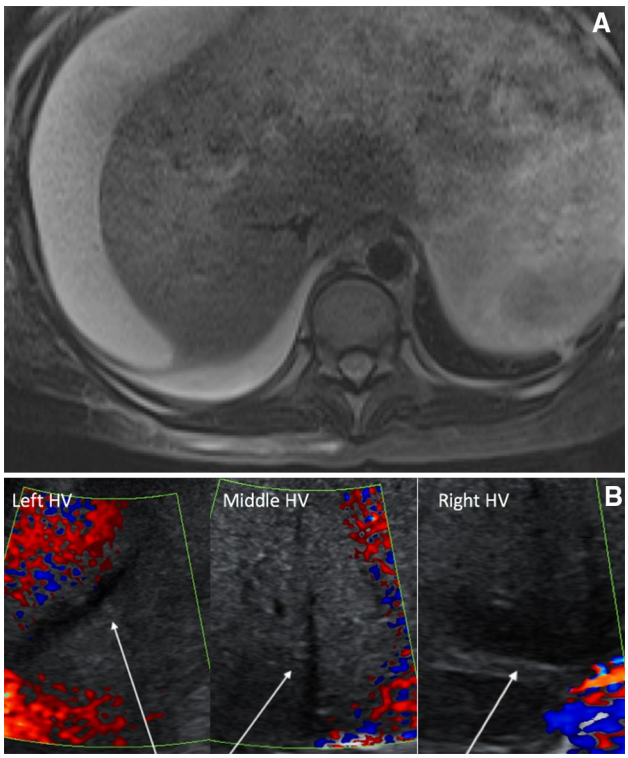

Fig. 6 Gadolinium-enhanced MRI of the liver in a female with a long history of OCP use and acute Budd–Chiari syndrome. Axial T2-weighted sequence **a** demonstrates peripheral areas of hepatic hyperintensity and ascites due to congestion. Normal hepatic vein flow voids are not visualised. **b** Colour Doppler ultrasound images confirm absence of flow in the occluded hepatic veins

The subacute form of BCS is the most common presentation of BCS in which there is insidious development of symptoms over months. Varying degrees of portal hypertension, ascites and hepatic failure are present [31]. On MRI, hypo-perfused areas of the liver are hypo-enhancing [32] (Fig. 7), however, the development of collateral veins may result in a more homogeneous pattern of enhancement [31].

In the chronic presentation, manifestations of portal hypertension predominate, namely—splenomegaly, varices and ascites. Portosystemic collateral vessels and hepatic artery enlargement may be seen. Intrahepatic collaterals connect the patent portion of the obliterated hepatic vein with either a normal vein, an accessory vein or the caudate lobe vein, which drain directly into the IVC [34]. The IVC and hepatic veins may not be visible due to compression by compensatory caudate hypertrophy or collapse related to diminished flow [24] (Fig. 7).

The enhancement pattern seen with the liver is variable. Morphological changes of the liver include caudate hypertrophy, contour irregularity and atrophy of the peripheral segments. The parenchymal oedema is replaced by fibrosis which results in decreased T1 and T2-signal on nonenhanced MRI and in delayed enhancement on post-contrast sequences [31]. Development of large regenerative nodules may occur as there is compensatory nodular hyperplasia in the areas of the liver with preserved hepatic venous outflow [32].

Portal vein thrombosis

Portal vein thrombosis (PVT) is characterised by interruption of normal blood flow in the portal vein due to blood clot. The most common cause of PVT is liver cirrhosis with

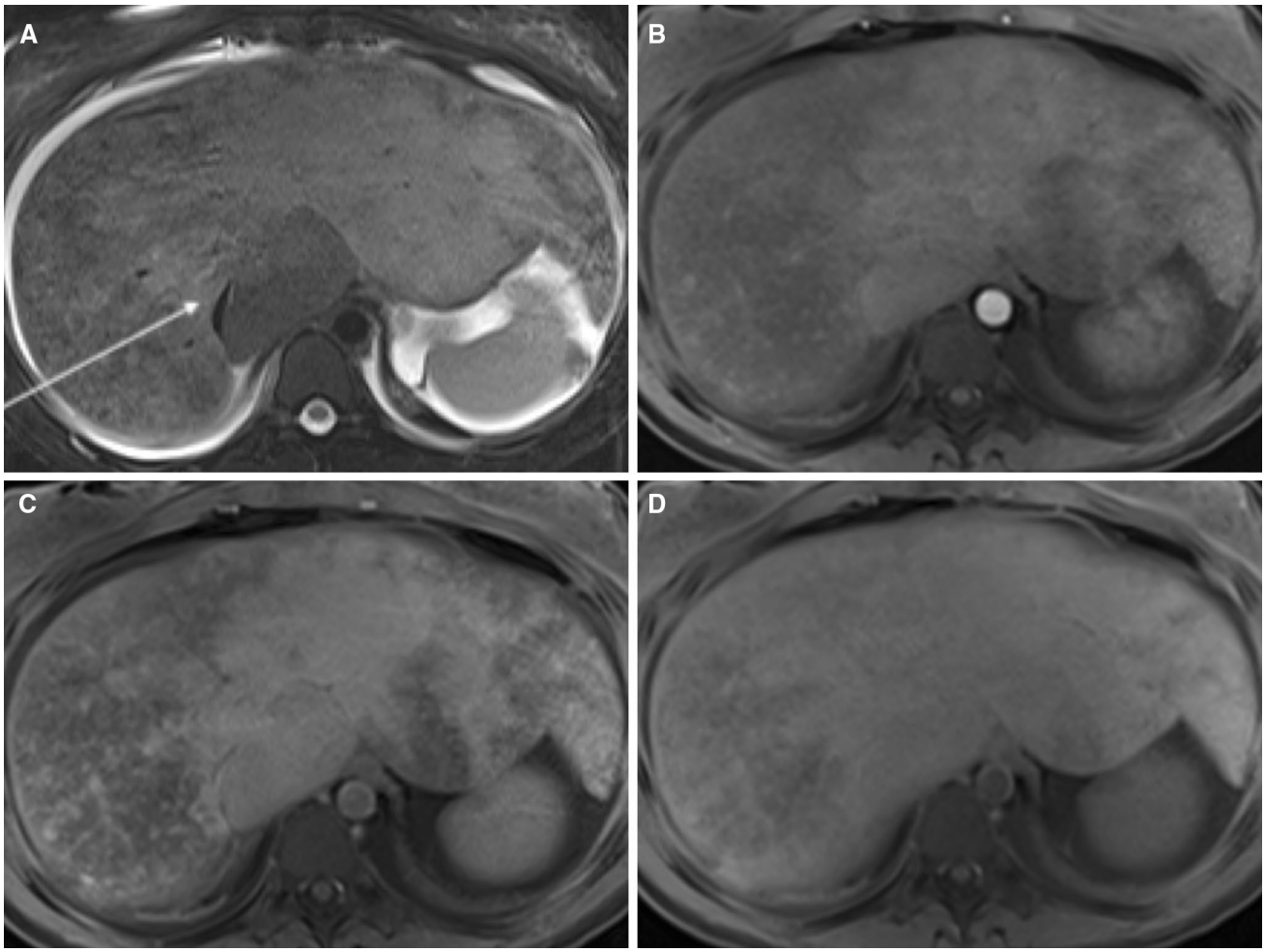

Fig. 7 Gadolinium-enhanced MRI of the liver in a young female on the OCP with subacute Budd–Chiari syndrome. Axial T2-weighted sequence **a** demonstrates heterogenous T2-hyperintensity in the liver with sparing and hypertrophy of the caudate lobe (arrow) which compresses the IVC. In the arterial **b** and portal venous phases **c**, there is enhancement of the central liver. Heterogeneously, hypo-enhancing areas in the periphery demonstrate progressive enhancement in the delayed phase **d,** which occurs in the initial phase of the 'flip-flop' pattern of enhancement although the complete pattern is not seen in this case. The hepatic veins do not enhance and ascites is noted

hepatocellular carcinoma [35]. PVT may also occur as a primary vascular disorder without liver disease, in the context of prothrombotic conditions including in the setting of oral contraceptives [36].

In acute PVT, the main clinical presentation is abdominal pain, however, there may be no symptoms if the portal venous obstruction is partial. It may either recanalize or become chronic, in which case, symptoms relate to development of portal hypertension, such as ascites and variceal bleeding [37].

On MR, acute thrombus might be T1-isointense to hyperintense. The portal vein may be expanded [38]. After intravenous contrast, there is partial or complete non-enhancement which may extend into the splenic or superior mesenteric veins [35]. Edge enhancement may be seen, which is related to either blood flow around the thrombus or an inflammatory response of the venous wall. Periportal T2-hyperintensity may also be evident.

In a chronically thrombosed portal vein, the portal vein may not be visualised as it is obliterated or attenuated (Fig. 8). Cavernous transformation of the portal vein involves numerous collateral veins forming in the hepatic hilum (Fig. 8). Venous collateral may be small and indistinct, producing a mass-like 'portal cavernoma', which may simulate malignancy or lymphadenopathy. It has been attributed to abundant fibrosis around individual periductal veins [38].

When portal blood flow is reduced, the hepatic artery dilates (Fig. 8) leading to perfusion abnormalities with increased hepatic enhancement in the arterial phase and decreased enhancement in the portal venous phase. The increased hepatic arterial blood supply may also promote formation of nodular regenerative hyperplasia and focal

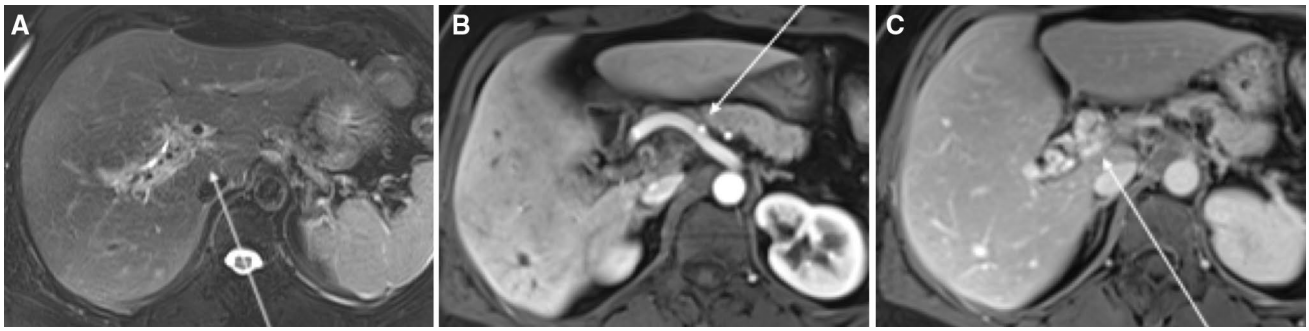

Fig. 8 Gadolinium-enhanced MRI in a patient with chronic portal vein thrombus on long-term oral contraceptives. Axial T2-weighted sequence **a** demonstrates an absent flow void in the portal vein with periportal T2 hyperintensity and small flow voids representing collateral vessels. Arterial phase T1-FS sequence **b** displays hepatic artery dilatation. In the portal venous T1-FS sequence **C** there is evidence of cavernous transformation of the portal vein with multiple enhancing collateral vessels in the hepatic hilum

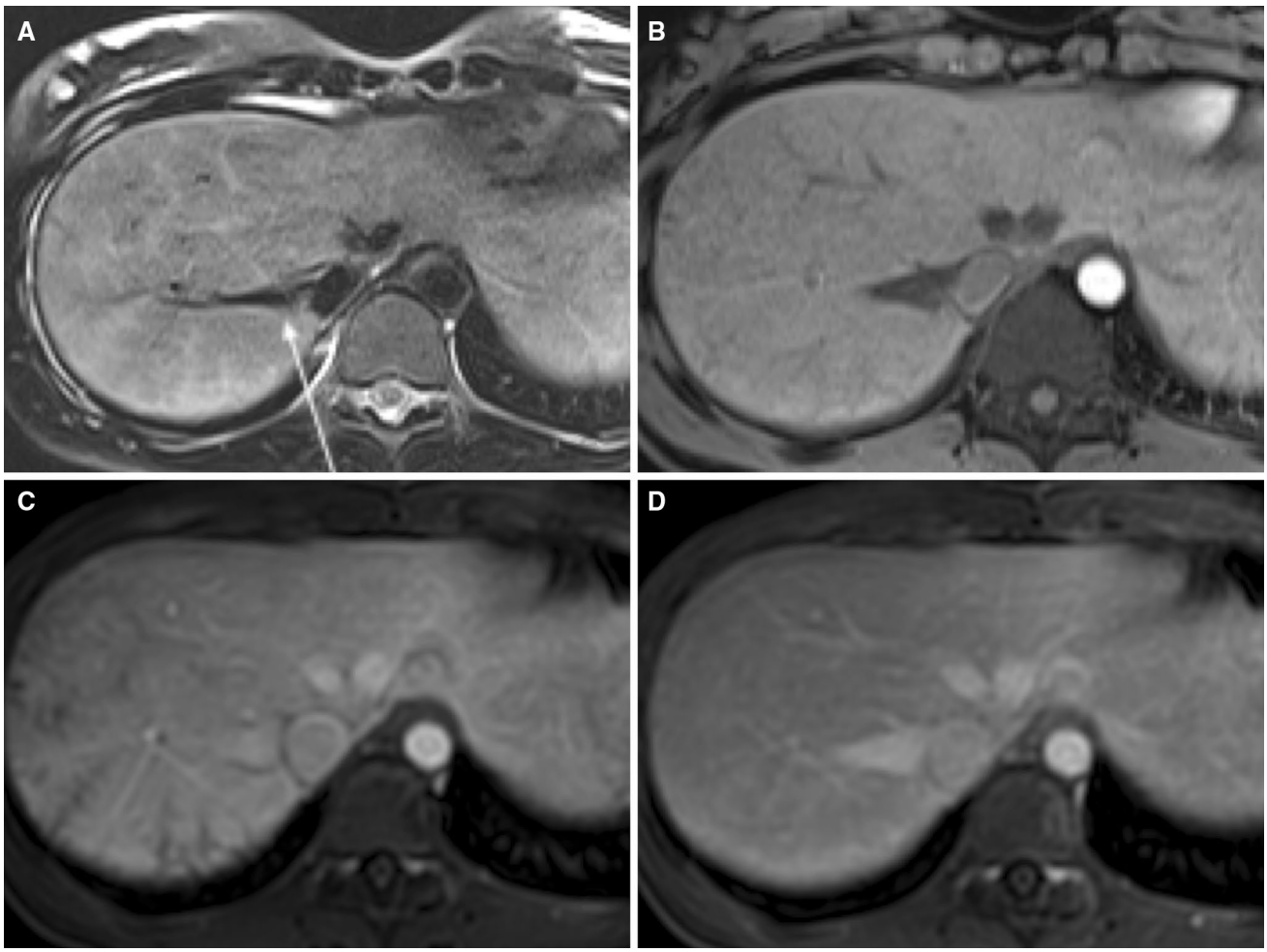

Fig. 9 Gadolinium-enhanced MRI in a young female on the OCP with right upper quadrant pain and biopsy proven veno-occlusive disease. Axial T2-weighted sequence **a** demonstrates normal flow voids in the hepatic veins (arrow) and heterogenous areas of T2 hyperintensity. Arterial phase **b** and portal venous **c** sequences show heterogeneous enhancement without caudate nor central sparing. In the delayed phase **d**, the heterogeneous enhancement becomes less apparent. There is normal enhancement of the hepatic veins

nodular hyperplasia-like nodules. The liver may undergo central hypertrophy. Areas of capsular retraction and fibrosis on the liver surface may be seen [38].

Veno-occlusive disease

Veno-occlusive disease, also known as hepatic sinusoidal obstruction syndrome, is a rare but life-threatening clinical syndrome characterised by painful hepatomegaly, ascites and hyper-bilirubinaemia [39]. It is a disorder of hepatic venous outflow obstruction that occurs at the level of the small post-sinusoidal venules initiated by endothelial lining injury [40]. It may be considered as a distinct entity to Budd Chiari Syndrome, characterised by different aetiological features, imaging characteristics and treatment options [41]. The condition was originally attributed to drinking bush-tea in Jamaica, however, is now known to be associated with many causes such as chemotherapy and oral contraceptives [39].

Sinusoidal congestion results in a heterogeneous appearance to the liver [42] with areas of decreased T1-signal and increased T2-signal on MRI [41]. On post contrast sequences, there is patchy enhancement [43] which is often decreased and delayed (Fig. 9). Unlike in BCS, the findings in veno-occlusive disease involve the entire liver without central sparing or caudate sparing as the outflow obstruction occurs at the level of the post sinusoidal veins. All hepatic segments are affected equally with no central predominant enhancement nor hypertrophy [41].

In contrast to BCS, the hepatic veins and IVC remain patent although they may be compressed due to the hepatic congestion. In addition, enhancement of the hepatic veins may be delayed due to congestion and secondary portal hypertension [41]. Other findings include periportal oedema, ascites and gall bladder wall thickening [39].

Conclusion

The oral contraceptive pill and anabolic steroids are exogenous sex steroids that may also induce hepatic tumours and a number of vascular disorders in the liver, some of which may be life-threatening. Knowledge of these conditions, their association with these hormones and their imaging features allows timely diagnosis and management of such disorders, which are seen in an otherwise young and healthy population.

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Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest.

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