

# Hepatic malformations: morphogenetic, anatomical and pathological features

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## SUMMARY

Hepatic organogenesis is a complex process involving various molecular and cellular determinants. Knowledge of the anatomical and functional structure of the liver and its relationship with other abdominal organs is fundamental from a surgical point of view. Clinical autopsies were performed upon twelve fetal specimens. Photographic footage was reviewed for fetal livers presenting macroscopic abnormalities, and relevant cases were included. A search was conducted employing terms pertaining hepatic malformations' morphogenetic, anatomical and pathological features. A thorough review was elaborated introducing an updated classification based on autopsy findings and available literature. Twelve fetal specimens underwent clinical autopsies. Gestational age ranged between 18 and 38 weeks (mean 28 weeks). All livers displayed symmetrical lobes. Seven of them presented at least one dysmorphic feature on macroscopic examination. Hepatic malformations can be classified into anomalies due to excessive development, defective development or extrinsic factors. The relevance of the proper identification of liver malformations lies in the broad spectrum of clinical

manifestations with different degrees of morbidity associated with them.

**Key words:** Liver – Morphogenesis – Abnormal lobulation – Accessory lobe – Autopsy

## INTRODUCTION

Hepatic organogenesis is a complex process involving diverse molecular and cellular determinants, which interact to establish the fate of the definitive endodermal cells of the four-week embryo towards the formation of the parenchyma and stroma of the liver (Severn, 1972; Si-Tayeb et al., 2010; North and Goessling, 2011; Gordillo et al., 2015).

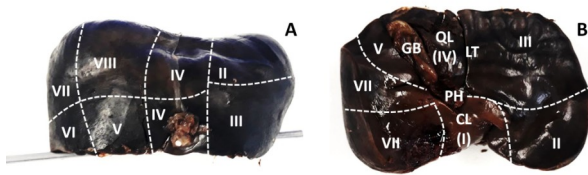
Cantlie was the first to recognize the divergence between anatomical lobulation and functional segmentation of the liver. In 1954, Couinaud described with greater detail the distribution of the parenchyma in four sectors demarcated by imaginary planes corresponding to hepatic veins' axes (Emond and Renz, 1994; Chin et al., 2018) (Fig. 1). At the microscopic level, hepatocytes are strategically arranged in order to carry out metabolic and biotransformation reactions (Diehl-Jones and Askin, 2002; Grijalva and Vakili, 2013).

Precision in anatomical descriptions has led to identification of variable expressions in the configuration of hepatic lobes and their relationships with other intra-abdominal structures. However, from the surgical point of view, recognition of abnormali-

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**Fig 1.** Functional segmentation of a 24-week fetal liver. (A) Anterior surface. Vertical lines corresponded to axes drawn by the trajectory of hepatic veins, which demarcate four sectors, each one comprising two segments. (B) Inferior surface. GB, gallbladder; QL, quadrate lobe; LT, ligamentum teres fissure; PH, porta hepatis or hepatic pedicle; CL, caudate lobe or segment I.

ties and normal anatomical variants becomes relevant, since they can eventually translate into clinical manifestations with different degrees of morbidity (Champetier et al., 1985; Kurniawan et al., 2017).

In contrast, there are several macroscopic characteristics that must be recognized and properly described during an autopsy in order to elaborate an accurate depiction of major and minor malformations, which are crucial for the definition and understanding of complex syndromes. In the exercise of perinatal pathology, macroscopic features of morphological abnormalities of the liver are insufficiently described, as well as their pathological associations, reminding us that the brain only understands what the eye is trained to see.

**MATERIALS AND METHODS**

Clinical autopsies were performed upon twelve fetal specimens referred to our institution between October and November 2018. Prior maternal consent was obtained and select cases authorized donation of cadaveric tissue, in accordance with the WMA Declaration of Helsinki Guidelines. Fetal livers were inspected, and macroscopic abnormalities were described. Photographic footage required for expert pathology report was reviewed, and fetal livers presenting relevant malformations were included in the present work. Visual material was edited in order to remove information possibly leading to identification of the patient.

A search was conducted on Pubmed, EMBASE and Scielo databases employing terms pertaining to hepatic malformations’ morphogenetic, anatomical and pathological features. Results were filtered based on title and abstract without language or year limitation. Reviews, original articles and case reports were included. A thorough review was elaborated introducing an updated classification based on autopsy findings and existing literature.

**RESULTS**

Twelve fetal specimens (n = 12) underwent clinical

**Table 1.** Frequency of hepatic malformations documented among twelve fetal specimens which underwent clinical autopsies.

Anomaly	Frequency (n =12, %)
Sessile/pedunculated accessory lobes	3/12 (25)
Pons hepatis	2/12 (16. 6)
Rouvière’s fissure	1/12 (8.3)
Hypertrophic papillary process	1/12 (8.3)
Corset liver	1/12 (8.3)
Deep diaphragmatic sulci	1/12 (8.3)
Thoracic projection (diaphragmatic hernia)	1/12 (8.3)

autopsies. Gestational age ranged between 18 and 38 weeks (mean 28 weeks). All livers displayed symmetrical lobes. Seven of them presented with at least one dysmorphic feature on macroscopic examination. Malformations observed included: sessile/pedunculated accessory lobes (25%), pons hepatis (16. 6%), Rouvière’s fissure (8.3%), hypertrophic papillary process (8.3%), corset liver (8.3%), deep diaphragmatic sulci (8.3%) and thoracic projection in the context of diaphragmatic hernia (8.3%) (Table 1).

**DISCUSSION**

**Hepatic Morphogenesis**

The liver originates from an endodermal diverticulum located in the ventral portion of the foregut’s caudal end at the fourth week of gestation (Severn, 1972; Grijalva and Vakili, 2013). Specification of endodermal cells towards their hepatic lineage gives rise to hepatoblasts. Molecular signals necessary for induction and liver differentiation arise from cardiogenic mesoderm and septum transversum’s mesenchyme (Si-Tayeb et al., 2010; North and Goessling, 2011). Expression and interaction of FGF-1/2, BMP-4, TGF-β, Prox1, Hippo and WNT/β-catenin pathways promote hepatocyte differentiation and hepatic cytoarchitecture determination by zones (Zhao and Duncan, 2005; Si-Tayeb et al., 2010; North and Goessling, 2011; Hassan et al., 2013; Yimlamai et al., 2014).

To form cellular cords, hepatoblasts undergo a process of epithelial-mesenchymal transformation. This process allows cell delamination and invasion of septum transversum’s mesoderm surrounding primordial vascular structures, which will later constitute the sinusoidal capillaries under the influence of vascular endothelial growth factor (VEGF) (Si-Tayeb et al., 2010). The umbilical vein constitutes the main afferent venous system of the developing liver’s angiogenesis center, and its function is later replaced by the portal vein. Meanwhile, the vitelline veins are part of the efferent system and contribute to hepatic veins’ formation (Severn, 1972; Delattre et al., 2000; Si-Tayeb et al., 2010;

Hirose et al., 2012).

By the sixth week of gestation, the tissue is colonized by hematopoietic cells from the yolk sac (Si-Tayeb et al., 2010; Hirose et al., 2012). During the fetal period, the liver increases in size and metabolism clearance and synthesis functions begin to mature, hence displacing the hematopoiesis towards the bone marrow (Diehl-Jones and Askin, 2002).

Other cell populations also participate in the consolidation of the parenchyma's definitive architecture (Table 2). For instance, under the influence of Wt1 and retinoic acid, precursors of stellate cells regulate liver growth. Any disruption in this pathway may result in hypoplasia (Si-Tayeb et al., 2010). Relationship with adjacent organs lying in proximity such as the heart, diaphragm, stomach, colon, umbilical cord, abdominal wall, right kidney and adrenal gland, in a fixed volume within the abdominal cavity accounts for the liver's surface anatomy (Hirose et al., 2012) and can explain the artificial forms acquired with altered spatial disposition, as is the case for abdominal wall defects and diaphragmatic hernias (Feist and Lasser, 1959; Ito et al., 1999).

### Normal Architecture

Throughout embryonic and fetal periods, the liver increases proportionally in diameter and length (Tongprasert et al., 2011; Szpinda et al., 2015; Paruszewska-Achtel et al., 2018). By gestational

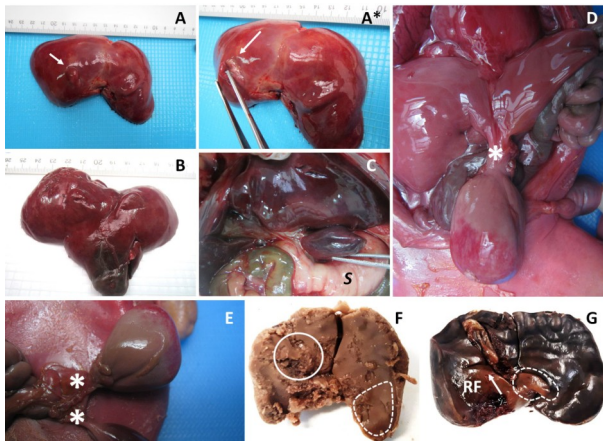
day 60, it corresponds to 10% of fetal weight. As hepatic hematopoiesis is displaced to other organs, the parenchyma regresses and the liver constitutes about 5% of the body weight in the newborn and 2.5% in the adult (Delattre et al., 2000), suggesting it is only possible to appreciate the liver's definitive appearance in mature individuals (Emond and Renz, 1994; Parke et al., 1996; Si-Tayeb et al., 2010).

In the newborn, both lobes are of similar dimensions and symmetrical. During hepatic maturation, the lower rim of the left and right lobes loses about two thirds and one third of its caudal extension, respectively. Hence, the gallbladder, which is largely covered by parenchyma between gestational weeks 10 and 17 (Fig. 2F), becomes more superficial and exceeds the hepatic margin (Parke et al., 1996; Wang et al., 2012). The definitive proportions are achieved around the eighteenth month of extra-uterine life (Rocha et al., 2009).

The liver is constituted by four anatomical lobes: right and left separated by the falciform ligament; caudate, between the inferior vena cava (IVC) and the ligamentum venosum; and quadrate, between the fissure of the gallbladder and the groove of ligamentum teres (Emond and Renz, 1994; Delattre et al., 2000; Diehl-Jones and Askin, 2002). There are four functional sectors divided by vertical planes, which correspond to hepatic veins' trajectories. Each sector is divided into two segments according to the portal vein branching. The right

**Table 2.** Main cellular components of the fetal liver and their role in hepatic organogenesis.

Cellular component	Role in organogenesis
Hepatocytes	70% of mature liver parenchymal cells Differentiate from hepatoblasts that proliferate within the septum transversum and form organized cords around developing sinusoids Metabolic and clearance function
Cholangiocytes	3% of mature liver parenchymal cells Differentiate from bipotential hepatoblasts with biliary phenotype The ductal plate undergoes a remodeling process beginning at week twelve, resulting in the formation of intrahepatic bile ducts
Vascular endothelial cells	Participate in the formation of veins, arteries, venules and arterioles
Sinusoidal endothelial cells	2.5% of mature liver parenchymal cells Differentiate from the endothelium of the vitelline veins and the septum transversum Become structural basis for the establishment of hepatic cellular cords Important hematopoietic function during fetal life
Kupffer cells	15% of mature liver parenchymal cells Originate from the yolk sac and later from the bone marrow Hepatic macrophages of the phagocytic mononuclear system family Participate in fetal erythropoiesis
Stellate cells (Ito)	1.4% of mature liver parenchymal cells Originate from the proepicardium and septum transversum mesoderm Reside in the perisinusoidal space (of Disse) and store lipids and vitamin A Modulate hepatic morphogenesis through the synthesis of retinoic acid Can be activated to myofibroblasts (cells with fibrogenic potential)
Hematopoietic cells	Transitory, appear towards the sixth or seventh week of gestation The liver constitutes the main hematopoietic organ until the beginning of the third trimester (weeks 24 to 32) Participate in the maturation of hepatocytes owing to the secretion of oncostatin M, which activates the signaling cascade responsible for the expression of some metabolic enzymes



**Fig 2.** Malformations due to excessive development. (A, A\*) Bilateral sessile small accessory lobes (White arrow). (B) Sessile linguliform accessory lobe dependent of the anterior margin of the liver. (C) Ectopic tissue dependent of the lesser omentum in proximity to the lesser curvature of the stomach, may simulate intramural gastric tumor (S). (D, E) Accessory lobes attached to the main parenchyma by a vasculobiliary pedicle (\*). (F) Fetal liver, 18 weeks of gestation. No gallbladder was observed in the superficial plane (white circle). A sessile accessory lobe was observed in the posterior aspect of the left lobe (dotted line). (G) Fetal liver, 24 weeks of gestation. Rouvière's fissure (RF) was observed in the right lobe (white arrow) presenting papillary process hypertrophy of the caudate lobe (dotted line).

lobe has an anterior sector comprising a caudal (V) and cranial (VIII) segment; and a posterior sector, which in turn, has a caudal (VI) and cranial (VII) segment. The left lobe is formed by a postero-lateral sector constituted by a cranial segment (II) and an anteromedial sector which encompasses an anterior and caudal segment (III) and a medial segment (IV), which corresponds in great propor-

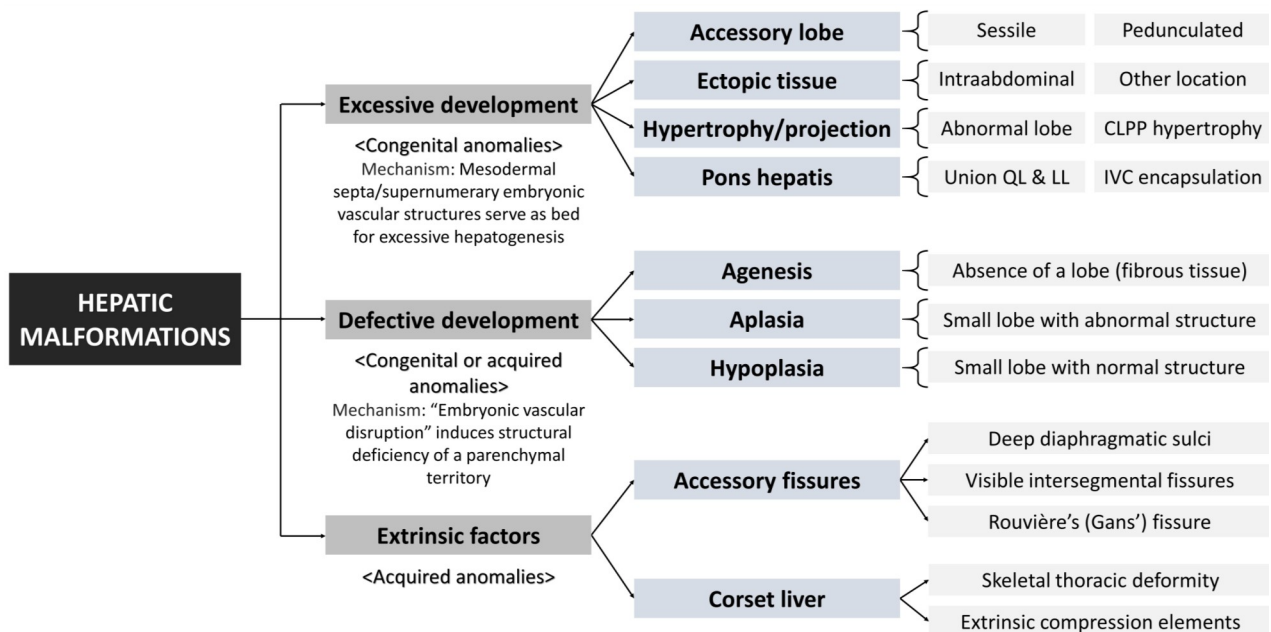
tion to the quadrate lobe. Segment I, or caudate lobe, is the only anatomical segment with an independent vascular pedicle (Emond and Renz, 1994; Delattre et al., 2000) (Fig. 1).

Three quarters of the hepatic blood flow arise from the portal vein and the remaining quarter from the hepatic arteries (Emond and Renz, 1994). Venous drainage depends on the hepatic veins: the right one drains a great portion of the right lobe, while the middle and left veins drain the rest of the parenchyma towards the IVC through a common trunk. The liver in situ is supported by folds of peritoneum that suspend it from the anterior wall (falciform ligament), diaphragm (triangular/coronary ligaments), stomach and duodenum (lesser omentum) (Emond and Renz, 1994; Delattre et al., 2000; Diehl-Jones and Askin, 2002; Geerts et al., 2008).

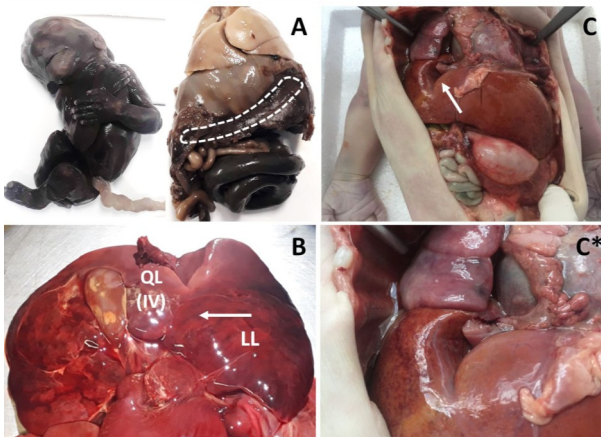
**Hepatic Malformations**

Congenital anomalies of the liver are rare (Champetier et al., 1985; Si-Tayeb et al., 2010; Hassan et al., 2013; Chaudhari et al., 2017; Chin et al., 2018). The earliest remarks on its anatomical alterations date back to the first decades of the 19th century (Cullen, 1925). According to their etiology and pathophysiological mechanism, malformations can be grouped into three categories, adapted from the classifications proposed by Jacquemet (1896) and Champetier et al. (1985) (Fig. 3).

The first group corresponds to alterations caused by excessive development and includes: accessory lobes, ectopic liver tissue, hypertrophy or projections, and pons hepatis. The second group beholds the malformations due to defective deve-



**Fig 3.** Classification of hepatic malformations according to their etiology and pathophysiologic mechanism. Adapted from Jacquemet (1896) and Champetier et al. (1985). CLPP, caudate lobe papillary process; QL, quadrate lobe; LL, left lobe; IVC, inferior vena cava.



**Fig 4.** Malformations due to excessive development and extrinsic factors. (A) Dysmorphic fetus, 18 weeks of gestation. Right lateral thoracic tilt with decreased transverse diameter. Visceral block with evidence of a deep groove on the lateral aspect of the right lobe's convexity secondary to extrinsic compression or corset liver (dotted line). (B) Fetal liver, 38 weeks of gestation. Congestive appearance. Death due to hypoxia secondary to abruptio placentae in the context of severe preeclampsia. Pons hepatis was observed (white arrow) communicating quadrate with left lobe. QL, quadrate lobe; LL, left lobe. (C, C\*) Deep accessory fissure related to right diaphragmatic dome observed on the right lobe's convexity superior aspect (white arrow).

development, among which agenesis, aplasia and hypoplasia are described. The third group comprises anomalies triggered by extrinsic factors, such as accessory fissures and corset liver. The first two groups are considered to be congenital, while abnormalities due to extrinsic factors are usually acquired (Vinnakota and Jayasree, 2013).

#### *Anomalies Due to Excessive Development*

Accessory lobes are redundant segments of liver tissue in continuity with the main parenchyma, and their prevalence varies from 1% to 11.5% (Si-Tayeb et al., 2010; Kostov and Kobakov, 2011; Chin et al., 2018) (Fig. 2A-E). The most accepted theory regarding their etiology is persistence of mesodermal septa or superfluous vascular structures upon which the embryonic liver is capable of developing (Arakawa et al., 1984; Chaudhari et al., 2017; Corbitt et al., 2017). It is also suggested that they may originate as an independent bud of the hepatic diverticulum (Battle et al., 1979).

Most accessory lobes are infrahepatic and right-lobe dependent (Champetier et al., 1985; Glenisson et al., 2014). Consistent with their relationship to the main parenchyma, they are classified as sessile and pedunculated (Corbitt et al., 2017). The best-known example is Riedel's lobe, first described in the 19th century as a sessile linguliform projection of segments V and VI, most frequently observed in females, with a prevalence close to 3% (Battle et al., 1979; Si-Tayeb et al., 2010; Glenisson et al., 2014; Kurniawan et al., 2017; Chin et al., 2018).

In adult livers, accessory lobes can be classified into four groups according to their size: large pedunculated (> 31 g), small pedunculated (11 to 30 g), non-pedunculated/ectopic and punctate (< 10 g) usually dependent on the gallbladder wall (Corbitt et al., 2017; Kurniawan et al., 2017). These measures are still unknown in the pediatric population. Other expressions of excessive development are projections, which appear as an accentuation of the morphology of usual structures, as is the case of hypertrophic papillary process (Fig. 2G) (Singh, 2013).

Ectopic liver tissue is rare, with an incidence of less than 1%. It shares a similar etiology with accessory lobes, although post-traumatic hematogenous dissemination of hepatocytes has also been discussed (Rozen et al., 2011; Xu et al., 2012). It is most frequently found upon the gallbladder wall. Nevertheless, there are reports of heterotopic tissue located on the spleen, pancreas, adrenal glands, omentum, mediastinum, pericardium, myocardium, IVC and placental chorionic villi (Hassan et al., 2013; Stonko et al., 2018).

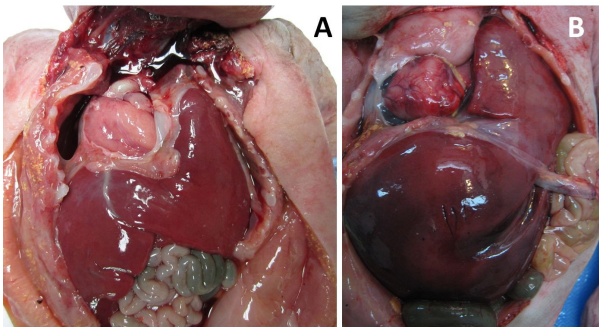
Another anomaly in this category is pons hepatis. This malformation corresponds to a parenchymal projection that connects two segments or lobes (Fig. 4B). In the classic presentation, the bridge communicates the quadrate lobe with the left lobe over the ligamentum teres fissure (Choy et al., 2013), even though it has also been described upon the liver's posterior aspect, encapsulating the vena cava (Chin et al., 2018).

#### *Anomalies Due to Defective Development*

Embryonic vascular disruption hypothesis postulates that alterations of venous supply can be an essential cause of liver malformations, while the absence or insufficiency of a normal afferent vein can induce structural deficiency (Champetier et al., 1985). Consequently, agenesis of a segment or lobe translates into complete absence of a portion of tissue, which is generally replaced by fibrous material. Aplasia refers to a lobe's insufficient growth with distorted cytoarchitecture. And hypoplasia denotes a portion of parenchyma with insufficient growth but no structural repercussions at the microscopic level (Wakefield, 1898; Champetier et al., 1985; Hassan et al., 2013). Atrophy of a lobe is typically accompanied by contralateral hypertrophy (Wakefield, 1898), since trophism of hepatic lobes is directly related to permeability of the afferent venous system (Champetier et al., 1985).

#### *Anomalies Due to Extrinsic Factors*

Pronounced accessory fissures are considered normal anatomical variants and are generally unremarkable from the clinical point of view. Their presence suggests the possibility of late intersegmental fusion (Si-Tayeb et al., 2010). The most frequent are diaphragmatic sulci in the convexity of the right lobe's lateral end (Fig. 4C-C\*), and Rou-



**Fig 5.** Congenital diaphragmatic hernia (A) Left lobe projection of the liver displacing heart and great vessels towards contralateral hemithorax. (B) Congestive liver and bowel protruding through left diaphragmatic defect.

vière's or Gans' fissure, also known as the sulcus of caudate process (Chin et al., 2018) (Fig. 2G).

In individuals with skeletal deformities or repetitive use of extrinsic compression elements upon the thoracoabdominal region, such as belts or girdles, a longitudinal indentation on the hepatic surface may generate a deep fibrous sulcus on the anterior aspect of the convexity of one or both lobes, receiving the name of corset liver (Glenisson et al., 2014) (Fig. 4A).

### Clinical Considerations

Most morphogenetic anomalies of the liver remain quiescent and are usually incidental findings in autopsies (Corbitt et al., 2017; Chin et al., 2018). The purpose of a detailed description of these variations is to provide an anatomical substrate to explain possible biases in diagnostic imaging and expand on differentials that should be taken into account in select clinical scenarios (Chaudhari et al., 2017).

Frequent findings in diagnostic imaging are accessory fissures, which under pathological conditions may lodge elements of different densities such as blood, pus or tumoral seedings. Due to the three-dimensional disposition, they can simulate intraparenchymal lesions such as hematomas, abscesses or tumors (Vinnakota and Jayasree, 2013; Chin et al., 2018).

Nearly 41% of pedunculated accessory lobes are related to abdominal wall defects including omphalocele, Beckwith-Wiedemann syndrome, umbilical hernia and cloacal exstrophy, as well as congenital diaphragmatic hernia and diaphragmatic agenesis (Johnstone, 1965; Loo et al., 2015; Corbitt et al., 2017) (Fig. 5). It has been noted they can interpose in the umbilical ring closure (Delattre et al., 2000; Hirose et al., 2012; Wang et al., 2012).

Furthermore, accessory lobes protruding into the thoracic cavity suspended by transdiaphragmatic pedicles can be misinterpreted as pulmonary nodules (Feist and Lasser, 1959; Babu and Van Der Avoirt, 2001; Tancredi et al., 2010) or pleural effusions causing respiratory distress in the newborn due to compression of lung parenchyma (Luoma

and Raboei, 2003). Hepatic masses can also displace the gastric chamber simulating intramural tumors (Battle et al., 1979) (Fig. 2C). In this setting, ectopic liver tissue has a greater potential for carcinogenesis, due to possible intrinsic metabolic alterations of the segment devoid of vasculobiliary drainage (Tancredi et al., 2010; Trocciola et al., 2011).

Pedunculated accessory lobes hanging from narrow pedicles are prone to be symptomatic owing to the risk of torsion and can present as acute abdomen requiring urgent surgical management (Bensaad and Algaba, 2017; Corbitt et al., 2017; Kurniawan et al., 2017). They may also present with rupture in traumatic lesions, generating intra-abdominal bleeding, torsion of the gallbladder, or acalculous cholecystitis if they lie in proximity (Corbitt et al., 2017; Kurniawan et al., 2017).

Aplasia or hypoplasia of the left lobe have been identified as risk factors for gastric volvulus, while insufficient development of the right lobe can progress to portal hypertension (Champetier et al., 1985; Singh, 2013; Chaudhari et al., 2017). It is important to bear in mind that among morphological alterations recognizable in perinatal autopsies are disruptions, sequences, deformities and changes by fixation, which can alter the expected appearance of the liver on macroscopic examination (Russo, 2007; Olaya Contreras, 2014).

### Conclusion

Even though the present work includes a small sample not powerful enough to generate statistically significant associations, it presents a diverse group of fetal liver specimens, which depicts accurately the wide spectrum of macroscopic hepatic malformations. The comprehensive description and classification of anatomical anomalies in liver development sheds light on clinical manifestations with different degrees of morbidity.

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