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Delayed development of the inferior mesenteric vein in human fetuses

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ABSTRACT

Background: The superior mesenteric vein appears as a fusion between irregularly-shaped slits of the midgut mesentery tissue at 5–6 weeks. In contrast, there might be no report when and how the inferior mesenteric vein (IMV) develops. We aimed to find the human initial IMV.

Materials and methods: We examined 1) sagittal histological sections of 7 human fetuses with 45-75 mm crown rump length or CRL (10–12 weeks); 2) horizontal sections of 15 fetuses with 70–155 mm CRL (12-18 weeks) and 3) horizontal sections of 12 late-term fetuses with 225–328 mm CRL (28–41 weeks).

Results: In the mesentery of the descending colon-rectum, the initial IMV lumen opened at 10–12 weeks of gestation, but the vein was difficult to trace upward to the anterior surface of the left adrenal. At 13–14 weeks, irrespective of whether it accompanied a colic artery, the IMV ran medially along the adrenal and it sometimes became thick near the pancreatic head. Earlier than the IMV, the middle colic vein appeared at the left aspect of the pancreatic head. Until late-term after establishment of the dorsal mesogastrium fusion with the mesocolon transversum, the IMV provided a peritoneal fold at the duodenojejunal junction.

Conclusions: A venous drainage via the IMV was much delayed possibly because, in early and midterm fetuses, an ongoing fusion of the midgut mesentery and a changing topographical relation among the abdominal viscera interfered with the venous flow. Instead, well-developed lymphatics seemed to be responsible for the drainage of the left-sided colon.

Keywords: inferior mesenteric vein, left adrenal, midgut mesentery, peritoneal fusion, left colic artery, human fetus

INTRODUCTION

Although it may be regarded as a vitelline vein derivative, most parts of the superior mesenteric vein later appear as a fusion between irregularly-shaped slits of the midgut mesentery tissue at 5–6 weeks of gestational week. This fact had already been described in [8] and it was recently ensured [6, 11]. Thus, the development occurs secondarily and independently from the vitelline vein. Being different from the superior vein, the bilateral vitelline veins does not run through the mesentery but in the peritoneal cavity at the almost entire course in early fetuses [6, 11]. In contrast, no study deemed to demonstrate when and how the inferior mesenteric vein (IMV) develops. In the present study, we aimed to find the human initial IMV.

A research group in the Netherlands presented excellent 3D-diagrams of the human early mesenteric vessels [3, 14], but they did not show the initial IMV. Likewise, Kim et al. [11] and Jin et al. [6] failed to find the IMV in their materials. According to Cho et al. [1], the IMV is underdeveloped in a long mesentery of the descending colon-rectum in early fetuses (15–39

mm CRL) before recovery of physiological herniation. In adults, the IMV takes unique courses above, along or behind the duodenojejunal junction and, therein, it often run through a peritoneal fold with considerable variations. The IMV drains into the splenic vein, superior mesenteric vein or portal vein. Those variations suggest that the IMV likely takes various laminar position at the fusion site between the mesocolon transversum and dorsal mesogastrium. The fusion occurs at midterm and continued to the late-term [5, 15]. Therefore, the IMV flow seemed to start at midterm or late-term after establishment of the mesenteric fusion and folding.

MATERIALS AND METHODS

The study was performed in accordance with the provisions of the Declaration of Helsinki 1995 (as revised in 2013). We examined histological sections from 1) 7 human fetuses with 45–75 mm crown rump length or CRL (sagittal sections; approximately 10-12 weeks of gestation); 2) 15 fetuses with 70–155 mm CRL (horizontal sections; approximately 12–18 weeks) and 3) 12 late-term fetuses with 225–322 mm CRL (horizontal sections; approximately 28–41 weeks). Table 1 shows the specimen numbers and sectional planes. The first and second groups of sections were serial and parts of the large collection kept at the Department of Anatomy of the Universidad Complutense, Madrid, and the resulting embryos were obtained from miscarriages and ectopic pregnancies from the Department of Obstetrics of the University. No information was available for genetic background of the embryos and/or abortion. The sections were stained with hematoxylin and eosin (HE) or azan. The use of the specimens was approved by the Ethics Committees of Complutense University (B08/374). All photographs were taken with a Nikon Eclipse 80.

The horizontal sections from 12 late-term fetuses were recently prepared by our group for studies of the retroperitoneal fusion [10]. These sections contained not only retroperitoneal tissues and organs but also the pancreas and upper parts of the descending colon including the left colic flexure. These fetuses were part of the collection of the Department of Anatomy, Akita University, Akita, Japan and were donated by their families to the Department in 1975–1985 and preserved in 10% w/w neutral formalin solution for more than 30 years. Data on

these specimens included the date of donation and the number of gestational weeks, but did not include the name of the family, obstetrician or hospital or the reason for abortion. Thus, the gestational age was estimated by sizes of the CRL as well as the maximum transvers length of the skull. The use of these specimens for research was approved by the Akita University Ethics Committee (No. 1428; the fourth author (G, M.) was one of the research member). Before a routine procedure for paraffin embedding, the specimens were decalcified by incubating them at room temperature in Plank-Rychlo solution ($AlCl_2/6H_2O$, 7.0 w/v%; HCl, 3.6; HCOOH, 4.6) for 3–7 days. The sections, all stained with HE, were semiserial (100-micron interval). All photographs of late-term histology were taken with a Nikon Eclipse 80.

Identification of artery and vein along and around the pancreas was based on Murakami et al. [13], Jeong et al. [5] and Jin et al. [7]. Sagittal sections were useful for tracing the candidate IMV upward toward the pancreas, while horizontal sections were much better than sagittal sections for identification of the connection between the candidate IMV and portal vein. In larger fetuses, however, the identification of the retroperitoneal IMV became easier even in horizontal sections because of the increased thickness (more details, see the head of the Results).

RESULTS

In specimens at 10–18 weeks, we identified the candidate initial IMV as a vascular lumen (or a series of lumens) containing red blood cells in the colic mesentery attaching to the left adrenal or posterior abdominal wall. To discriminate the candidate IMV from retroperitoneal veins such as adrenal and gonadal veins, we tried to trace upward the candidate IMV to a level in which the former vein was connected to a vein in or along the pancreas. In contrast, in later-term fetuses, we found the candidate IMV at and near the left colic flexure and paid attention to discriminate the latter from tributaries of the splenic vein. The splenic vein was easily found as a thick vein immediately behind or below the pancreas.

Sagittal serial sections of 7 human fetuses with at 10–12 weeks demonstrated the entire length of a left-sided mesentery from the splenic flexure, via the descending colon to the

rectum (Fig. 1). At the stage, the rectum was so long that it occupied a lower half height of the left-sided abdomen. The inferior mesenteric artery was seen running in the mesentery near the colon-rectum junction (Fig. 1A) and the arterial origin was located high in a level of the duodenum horizontal portion (Fig. 1G). Below the left adrenal, a longitudinal venous lumen was sometimes found (Fig. 1A, B; 3 of the 7 specimens), but we were difficult to trace upward the candidate IMV toward the left adrenal or pancreatic tail (Fig. 1C, D). Therefore, the IMV lumen opened first at the distal or lower course. The splenic vein was also thin but traceable toward the portal vein in or behind the pancreatic (Fig. 1D, E). A thickness of the superior mesenteric vein was almost same as the portal vein: thus, the latter appeared to be a continuation of the former (Fig. 1E, F). Finally, pelvic veins were dilated with blood retention, but they did not connect to the rectum without mesentery.

Horizontal serial sections of 15 fetuses at 12–18 weeks always exhibited the IMV candidate, with or without concomitant artery, in the left-sided mesentery on the left adrenal and/or kidney (Figs. 2, 3). However, the vein was usually cut transversely or obliquely and attached to the renal fascia (Figs. 2C, D and 3D, H). In contrast, the splenic vein was cut longitudinally or obliquely and appeared distant from the renal fascia. In 5 of the 15 specimens, we were able to find the IMV longitudinal course at and near the pancreatic head. The terminal longitudinal course of the IMV provided a peritoneal fold (3 specimens; Fig. 3C, G), but the fold appeared distant from the duodenojejunal junction. The longitudinally-cut terminal portion of the IMV did not accompany an artery (left colic artery or the other). Other than the IMV, thin veins were developing in a mesentery extending from the pylorus and transverse colon to the pancreatic head: they appeared to be the middle colic vein and/or the right gastroepiploic vein (Fig. 2D, F). The superior mesenteric vein was still almost thick as the portal vein. The left adrenal vein was very thick and separated from the IMV by a thick fascia (Figs. 2G, 3H). In addition, as reported previously [4, 17], a relatively large caudate lobe (Spiegel’s lobe) of the liver occupied in the lesser sac in front of the pancreas (Figs. 1E, F, 3C, D).

Horizontal sections of 12 late-term fetuses always show the IMV candidate in the left-sided mesentery on the left adrenal and/or kidney and, sometimes (3 of the 12), the vein ran

through a thick peritoneal fold at the duodenojejunal junction (Figs. 4, 5). The peritoneal fold, above or in the anterior side of the duodenojejunal junction, contained both the IMV and a candidate left colic artery (Fig. 4C) or the IMV only (Fig. 5B). In the medial side of the fold, the IMV took an almost straight course in the pancreatic head toward the portal vein (Figs. 4D, E, 5B). The concomitant artery ran along the left aspect of the pancreas to join one of the pancreaticoduodenal arteries. Both the left adrenal vein and splenic vein were much thicker than the IMV. The former veins were seen in the posterior side of the IMV and they were distant from the duodenojejunal junction. Along and in the pancreatic head, The IMV was still a bit thinner than the superior mesenteric vein (Fig. 5C). We did not find a peritoneal fold containing an artery only.

DISCUSSION AND CONCLUSIONS

The present study demonstrated a delayed development of the IMV in human fetuses: even at midterm, the venous lumen was much thinner than the superior mesenteric vein. In early and midterm fetuses, the ongoing rotation and fusion of the midgut mesentery seemed to interfere with the venous flow. Instead, well-developed lymphatics in the mesentery [9] might be partly responsible for drainage of the left-sided colon. However, venous blood retention gradually advances at the periphery and the hydrostatic power seemed to open a new venous lumen in the more proximally-located site. The venous flow seemed to increase at late-term and, simultaneously, the peritoneal fold became thick at the duodenojejunal junction. Laminar position of colic vessels in the retroperitoneal tissue at late-term was shown in our previous report [10].

The IMV drains into the portal vein, superior mesenteric vein or splenic vein in adults. This well-known variation at the IMV terminal seemed to be determined by timing, sequence and which part of the mesocolon transversum was folded and fused with the dorsal mesogastrium. The mesocolon is fused first at the pancreatic head at 8–9 weeks [15] and the middle colic artery becomes evident until 12 weeks [5]. The present study show a delayed development of the concomitant vein (Fig. 2F). In adults, multiple veins from the gastric antrum, transverse colon and duodenum usually join at the anterior aspect of the pancreatic

head to provide the gastrocolic venous trunk, which runs inferiorly to merge with the superior mesenteric vein [2, 12, 18].

The present figures demonstrated the left colic artery (abbreviated by “LCA”) along or near the IMV. However, territories of supply by the middle and left colic arteries show reciprocal variations: the left branch of the middle colic artery is likely to take over the splenic flexure of the left-handed colon [16]. Thus, some of the “LCA” were likely to be a branch of the middle colic artery. The initial peritoneal fold of the IMV (without a concomitant artery) formed at or near the pancreatic head (Figs. 2, 3). The medially-developed peritoneal fold might migrate laterally until late-term due to a drastic topographical change among upper abdominal viscera. Therefore, without a concomitant IMV, an artery was unlikely to make a peritoneal fold at the duodenojejunal junction.

We did not usually find the proximal course of the IMV near or at the pancreas (5/15 at midterm and 3/12 at late-term). In late-term fetuses, we did not deny a possibility that section interval (100-micron) contained the proximal course. However, in midterm fetuses, we suspected that a slight malrotation made our finding difficult. Cho et al. [1] found, in 11 of the 27 early fetuses, the descending colon outside of the abdominal cavity during physiological herniation. In these fetuses, the IMV opening seemed to be delayed than normal fetuses in which the ileum, cecum and ascending colon are outside.

ARTICLE INFORMATION AND DECLARATIONS

Data availability statement

The data that supported the findings of this study are available on request from the corresponding author.

Ethics statement

This study was performed in accordance with the provisions of the Declaration of Helsinki 1995 (as revised in 2013). This study was approved by Ethics Committees of Complutense University (B08/374) and Ethics Committees of Akita University (No. 1428).

Authors' contributions

CA Li: data acquisition and writing original draft. **JH Kim:** data analysis, figure lettering and draft review of the manuscript. **ZW Jin:** data analysis, manuscript editing and funding acquisition. **G Murakami:** design and data acquisition, prepare the figure lettering and writing and review manuscript. **JF Rodríguez-Vázquez:** data acquisition and critical revision of the manuscript. **S Hayashi:** review and critical revision of the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1. Specimens examined in the present study.

Age	Numbers examined	Sectional plane
10 weeks	2	Sagittal
11 weeks	2	Sagittal
12 weeks	3	Sagittal
	2	Horizontal
13 weeks	3	Horizontal

14 weeks	4	Horizontal
15 weeks	2	Horizontal
16 weeks	1	Horizontal
17 weeks	1	Horizontal
18 weeks	2	Horizontal
28–30 weeks	3	Horizontal
31–32 weeks	2	Horizontal
33–35 weeks	2	Horizontal
36–38 weeks	2	Horizontal
39–41 weeks	3	Horizontal

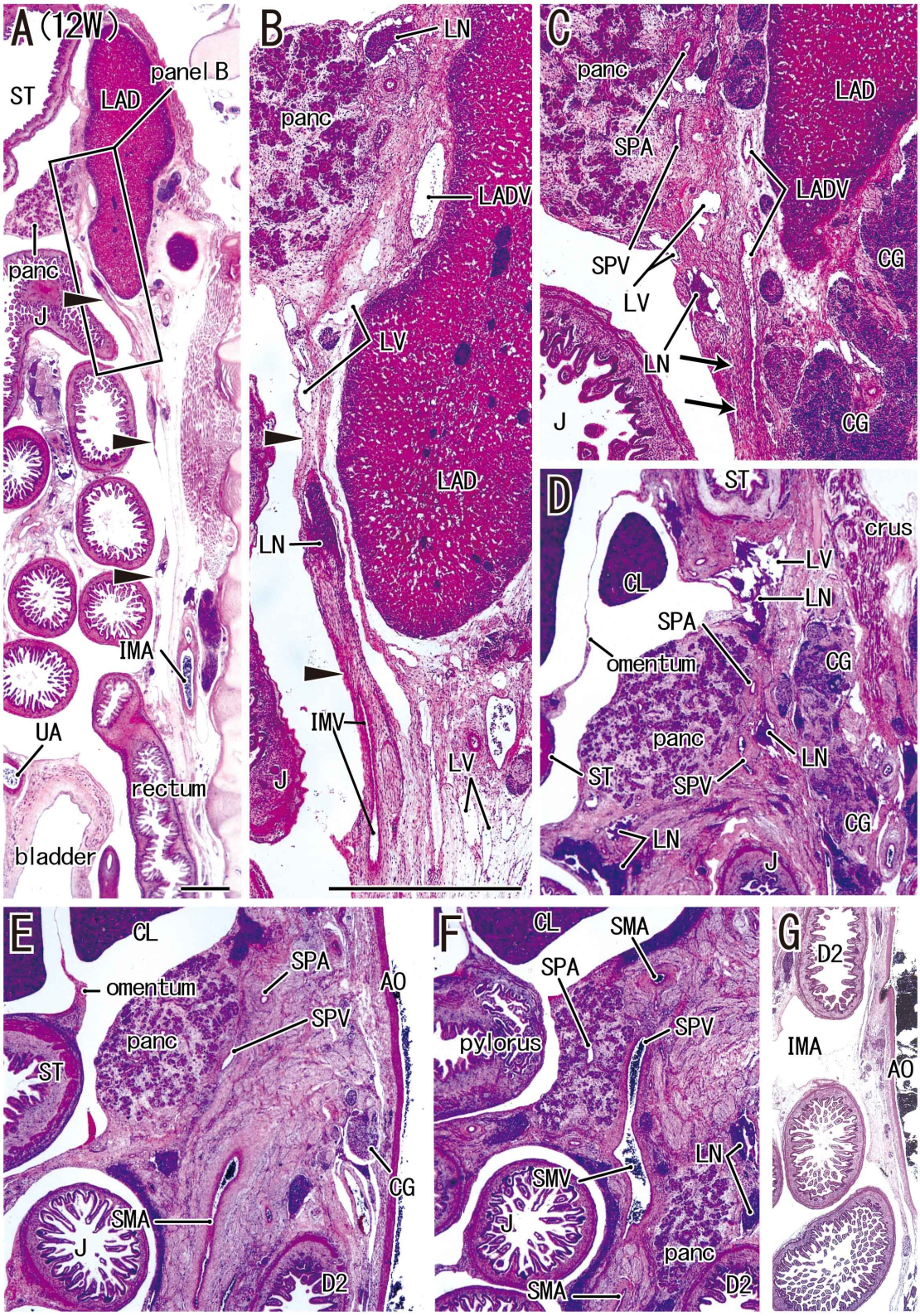

Figure 1. Initial IMV running upward in the descending colon mesentery and the splenic vein

approaching the superior mesenteric vein: sagittal sections at 12 weeks GA. **A, G.** The most lateral (or medial) plane. Panel A displays the entire length of the descending colon mesentery (arrowheads), the relatively long rectum and, the IMA. A square in panel A is shown in panel B at the higher magnification. **B–G.** Panels prepared at the same magnification: panels B–F exhibit distal-to-proximal courses of the splenic vein and a candidate initial IMV, while panel G displays the origin of the inferior mesenteric artery at the height of the duodenum horizontal portion (D2). The IMV is opened in panel B, but the venous lumen (double arrows) is almost closed near the left adrenal vein (LADV in panel C). The SPV approaches the SMV in panels D and E and joins the latter in panel F. The liver CL is separated from the other parts of the liver by the lesser omentum (omentum in panels D and E). Scale bars: 1 mm in panels A (×1 at objective) and panel B (×4 at objective). AO — aorta; CG — celiac ganglion; CL — caudate lobe of the liver; crus — diaphragmatic crus; D2 — D3 or D4 — second — third or fourth portion of the duodenum; IMA — inferior mesenteric artery; IMV — inferior mesenteric vein; J — jejunum; LAD — left adrenal; LADV — left adrenal vein; LN — lymph node; LV — lymphatic vessel; panc — pancreas; SPA — splenic artery; SPV — splenic vein; ST — stomach; UA — umbilical artery.

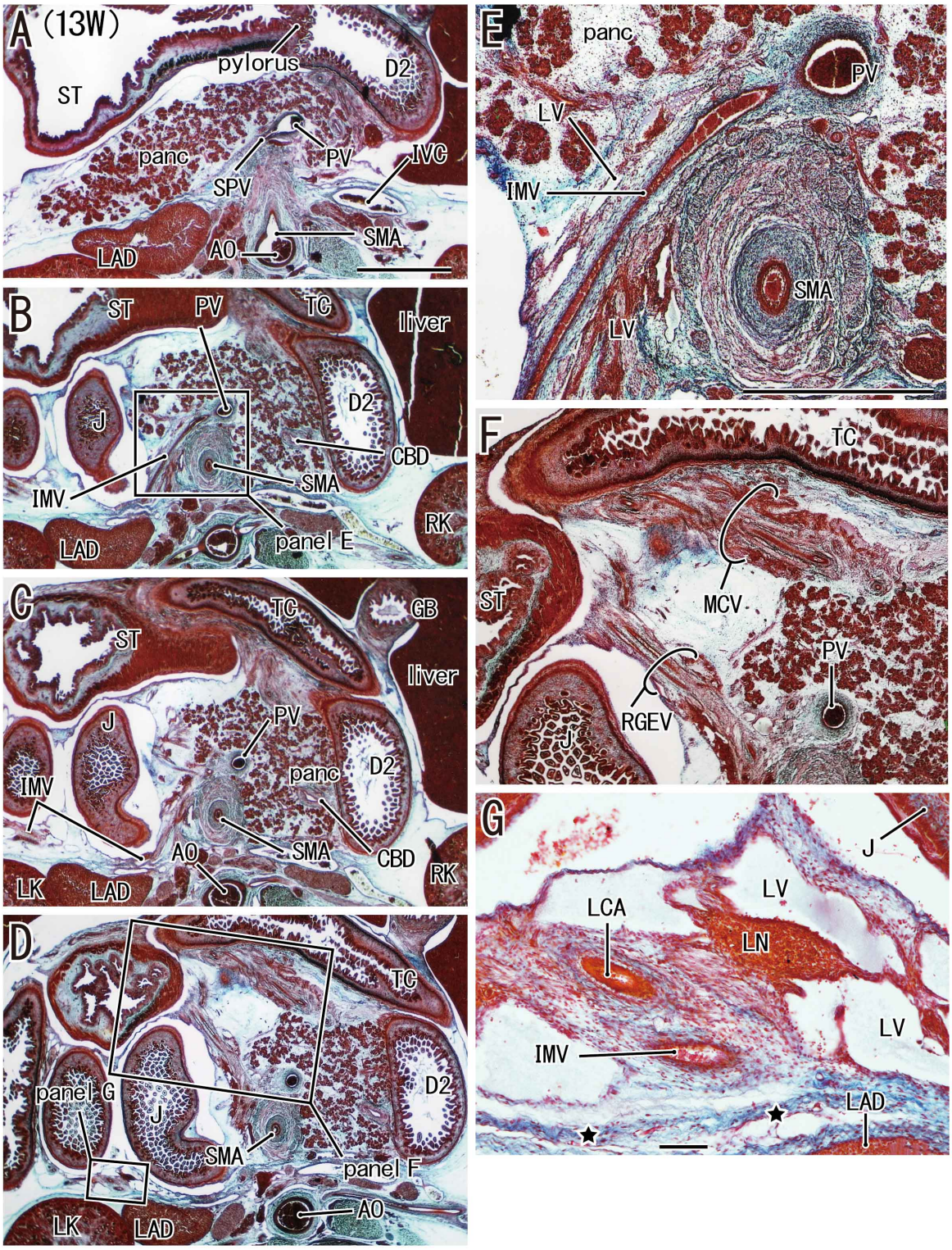

Figure 2. IMV running anteriorly along the left aspect of the superior mesenteric artery to

approach the portal vein: horizontal sections at 13 weeks. **A, D.** The most superior (or inferior) plane. Panel A, containing the SPV terminal at the PV, displays a plane 1.2 mm upper than the IMV terminal (panel B). **C, D.** The IMV is seen along the LAD. Squares in panels B and D are shown in panels E, G at the higher magnification. Panel E exhibits the terminal portion of the IMV. **F.** Two bundles of developing veins: the anterior bundle contains the MCV and the posterior one the RGEV. **G.** The LCA and IMV on the left adrenal. Stars indicate a thick fascia separating the IMV from the left adrenal. Panels A–D were prepared at the same magnification. Scale bars: 1 mm in panels A (×2 at objective) and panel E (×4 at objective), 0.1 mm in panel G (×10 at objective). AO — aorta; CBD — common bile duct; D2 — D3 or D4 — second — third or fourth portion of the duodenum; GB — gall bladder; IMV — inferior mesenteric vein; IVC — inferior vena cava; LAD — left adrenal; LCA — left colic artery; LK — left kidney; LN — lymph node; LV — lymphatic vessel; MCV — middle colic vein; panc — pancreas; PV — portal vein; RGEV — right gastroepiploic vein; RK — right kidney; SMA — superior mesenteric artery; SPV — splenic vein; ST — stomach; TC — transverse colon.

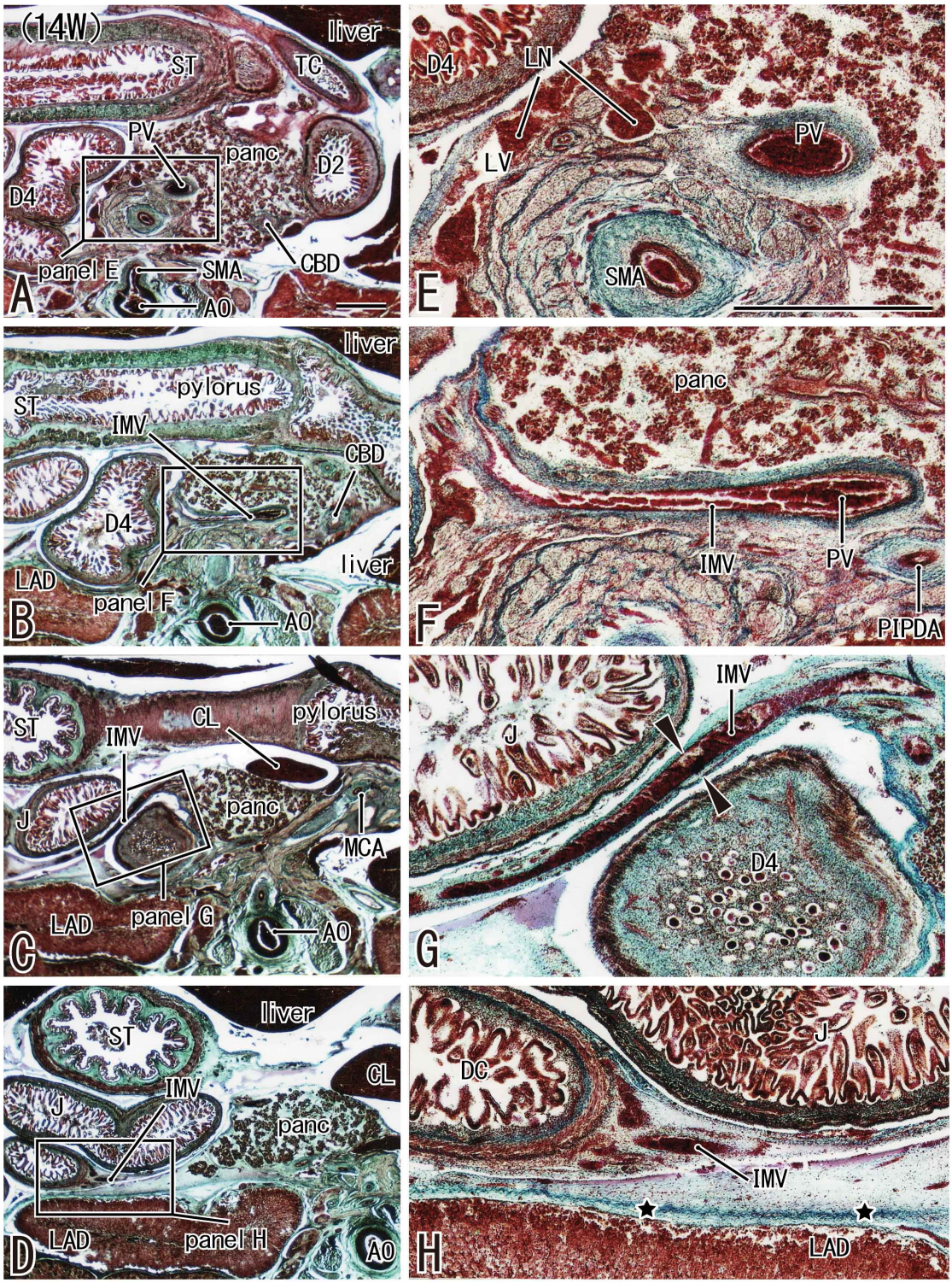

Figure 3. IMV running through a peritoneal fold near the duodenojejunal junction: horizontal

sections at 14 weeks. **A (or D).** The most superior (or inferior) plane. Panel A contains the origin of the SMA. **B.** The terminal portion of the IMV. **C.** Aperitoneal fold extending between the duodenum and jejunum. **D.** The IMV running along the LAD. **E–H.** Higher magnification vies of squares in panels A–D, respectively. In panel G, double arrowheads sandwich the peritoneal fold containing the IMV. In panel h, stars indicate a thick fascia separating the IMV from the left adrenal. The liver CL (in panels C and D) is separated from the other parts of the liver and attached to the pancreas. Panels A–D (or panels E–H) were prepared at the same magnification. Scale bars: 1 mm in panels A (×1 at objective) and panel E (×4 at objective). AO — aorta; CBD — common bile duct; CL — caudate lobe of the liver; D2 — D3 or D4 — second — third or fourth portion of the duodenum; DC — descending colon; IMV — inferior mesenteric vein; J — jejunum; LAD — left adrenal; LN — lymph node; LV — lymphatic vessel; MCA — middle colic artery; panc — pancreas; PIPDA — posterior inferior pancreaticoduodenal artery; PV — portal vein; SMA — superior mesenteric artery; ST — stomach.

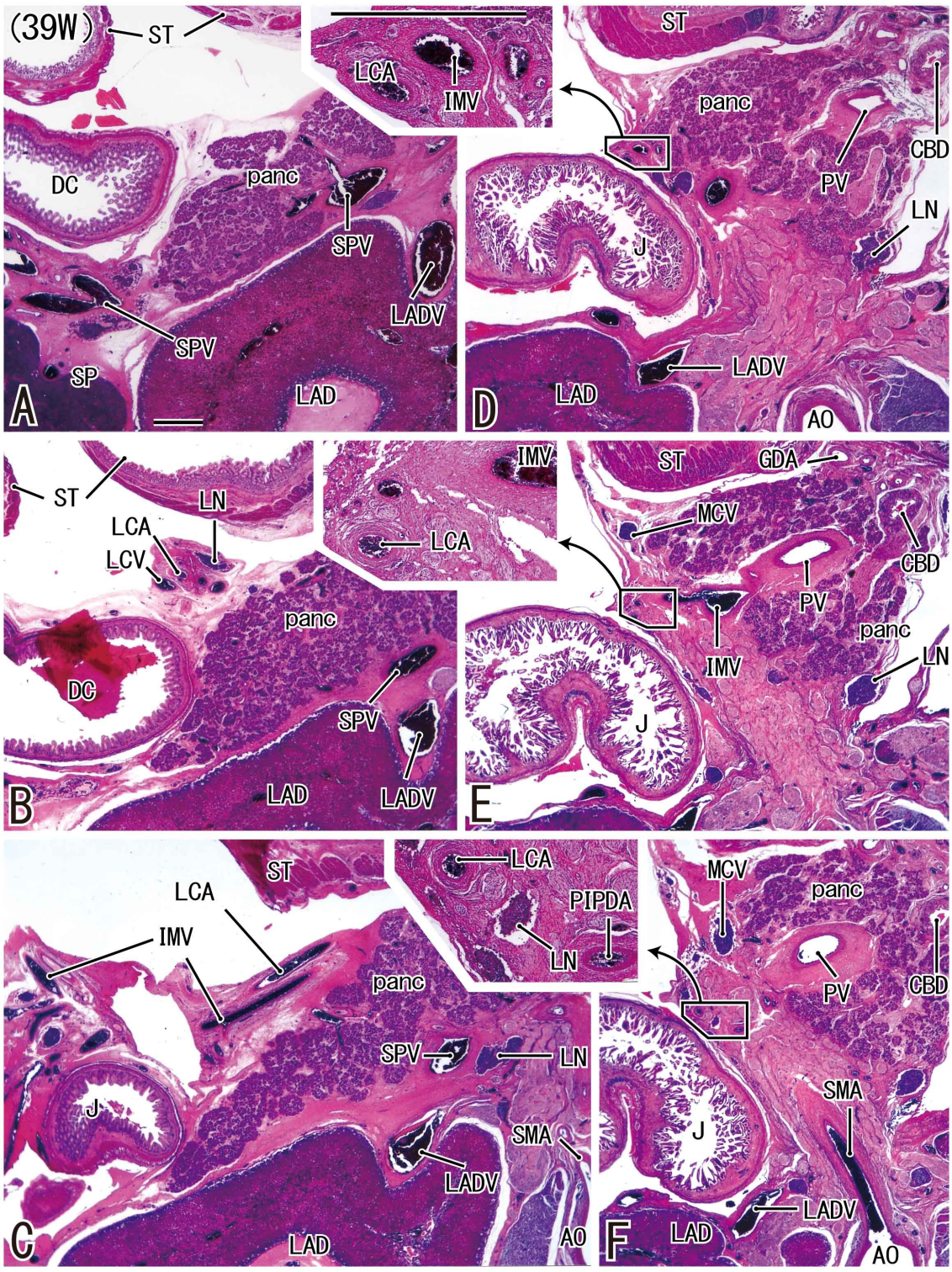

Figure 4. IMV accompanying the left colic artery on the anterior surface of the pancreas:

horizontal sections at 39 weeks. **A (or F).** The most superior (or inferior) plane. Panel A contains the spleen and peripheral parts of the splenic veins. **B, C.** The left colic artery and IMV running near and along the panc and, in panel **D**, the vessels reach the duodenojejunal junction. **E.** The terminal portion of the IMV near the PV. **F.** The origin of the SMA. Irregularly-shaped squares in panels D–F are shown in three inserts at the higher magnification, respectively. All panels (or Three inserts) were prepared at the same magnification (scale bar in panel A (×1 at objective) and the uppermost insert (×4 at objective), 1 mm). AO — aorta; CBD — common bile duct; DC — descending colon; IMV — inferior mesenteric vein; J — jejunum; LAD — left adrenal; LADV — left adrenal vein; LCA — left colic artery; LCV — left colic vein; LN — lymph node; MCV — middle colic vein; panc — pancreas; PIPDA — posterior inferior pancreaticoduodenal artery; PV — portal vein; SMA — superior mesenteric artery; SP — spleen; ST — stomach.

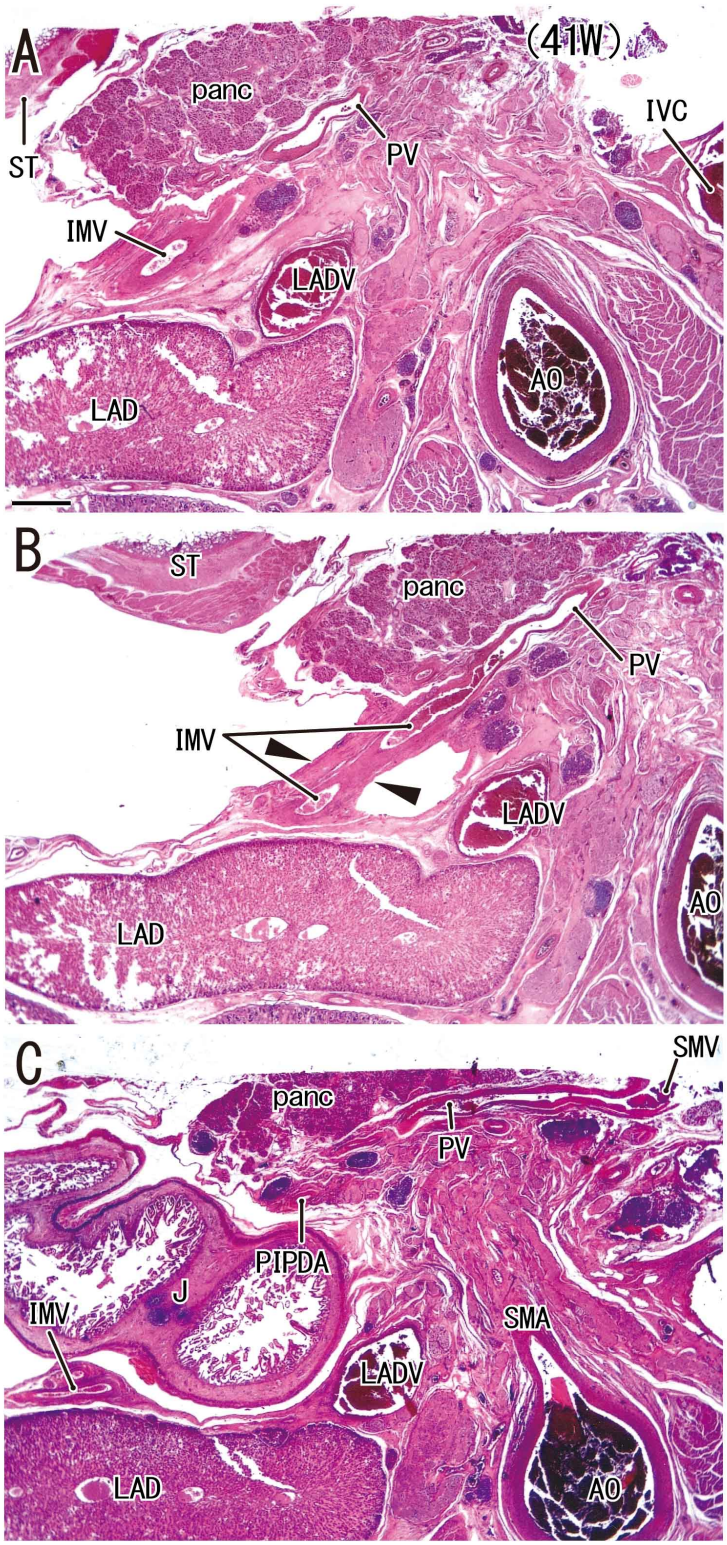

Figure 5. IMV passing through a thick peritoneal fold at the duodenojejunal junction:

horizontal sections at 41 weeks. **A (or C).** The most superior (or inferior) plane. Panel A displays the roof above the duodenojejunal junction. **B.** A thick peritoneal fold (double arrowheads) containing the IMV. **C.** The jejunum near the duodenojejunal junction as well as the portal vein connecting to the SMV. All panels were prepared at the same magnification (scale bar in panel A (×1 at objective, 1 mm). AO — aorta; IMV — inferior mesenteric vein; IMV — inferior mesenteric vein; IVC — inferior vena cava; J — jejunum; LAD — left adrenal; LADV — left adrenal vein; panc — pancreas; PIPDA — posterior inferior pancreaticoduodenal artery; PV — portal vein; SMA — superior mesenteric artery; SMV — superior mesenteric vein; ST — stomach.