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Original article

Portal hypertension: The desperate search for the placenta

Maria Angeles Aller[a,*], Natalia Arias[b], Javier Blanco-Rivero[c,d], Gloria Balfagón[c,d], Jaime Arias[a]

[a] Department of Surgery. School of Medicine, Complutense University of Madrid, 28040 Madrid, Spain
[b] Upper Third Floor, UCL Medical School, UCL Institute for Liver and Digestive Health, Royal Free Hospital, Rowland Hill Street, London NW· 2PF, UK
[c] Department of Physiology, School of Medicine, Autónoma University of Madrid, Spain
[d] Instituto de Investigación Sanitaria del Hospital Universitario La Paz (IdiPAZ), Madrid, Spain

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ABSTRACT

We propose that the circulatory impairments produced, in both portal hypertension and liver cirrhosis, to a certain degree resemble those characterizing prenatal life in the fetus. In fact, the left-right circulatory syndrome is common in cirrhotic patients and in the *fetus*. Thus, in patients with portal hypertension and chronic liver failure, the re-expression of a blood circulation comparable to fetal circulation is associated with the development of similar amniotic functions, i.e., ascites production and placenta functions, and portal vascular enteropathy. Therefore, these re-expressed embryonic functions are extra-embryonic and responsible for prenatal trophism and development.

1. Introduction

Increased venous pressure in the splanchnic venous system can reach pathological levels and induce complications, which in turn cause a higher morbidity and mortality rate in patients with hepatic insufficiency related to cirrhosis. Furthermore, Hypertension of the splanchnic venous system causes complications associated with an increased morbidity and mortality in the cirrhotic patients [1–3]. The splanchnic and systemic failure produced by portal hypertension resembles the beginning of shock. Both splanchnic and systemic hyperdynamic circulation increase and hence, cardiac output increases. Furthermore, the splanchnic hyperdynamic circulation induces dysbiosis. The subsequent hypoxia increases the angiogenic factor release, while also causing porto-systemic collateral circulation, mesenteric venous vasculopathy and even splenomegaly [4–7]. Vascular endothelial growth factor (VEGF) family and placental growth factor (PIGF) related [8–10] are the most important angiogenic factors causing splanchnic venous impairments.

In the vena cava drain, the collateral vessels are created from the coronary vein, the superior and middle hemorrhoidal veins, the umbilical vein, and the splenic vein. These first collateral vessels are called gastroesophageal veins, with varicose veins of the esophagus and upper stomach, the splenorenal veins, the para-rectal veins with haemorrhoids and the paraumbilical veins, which result in dilated veins in the anterior abdominal wall, thus making up a “caput medusa” [1,2]. Furthermore, an intrahepatic collateral circulation is produced by portal angiogenesis in the hepatic parenchyma, which transports the portal blood to the suprahepatic veins system [10,11].

It is obvious that increased pressure in the splanchnic venous system increases blood flow and, therefore elevates pressure to the systemic venous system [1,7]. In essence, elevated portal pressure, since it is arterialized by the hepatic and mesenteric arterial hyperdynamic circulation, makes portal blood flow carries its high pressure to the systemic venous system [12]. However, the creation of an alternative way of draining blood from the portal system to the systemic circulation could be pathophysiological more than the transmission itself of high pressure between two venous systems. An argument that favors the abovementioned hypothesis could be that portal pressure does not become normalized, despite decompression through the porto-systemic collateral circulation. Another hypothesized objective for the development of porto-systemic collateral circulation, could be favored by the systemic circulatory alterations of the cirrhotic patient, such as decreased peripheral vascular resistance, increased cardiac output and the opening of arteriovenous communications inducing the maintenance of the splanchnic hyperdynamic circulation and, therefore portal hypertension [13]. Consequently, the systemic and splanchnic response of the vascular bed to hemodynamic disturbances in portal hypertension is maladaptive. Nevertheless, beyond this

* Corresponding author at: Department of Surgery School of Medicine, Complutense University of Madrid, Ramón y Cajal s.n., 28040 Madrid, Spain.
E-mail address: maaller@med.ucm.es (M.A. Aller).

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mechanical explanation, the development of a porto-systemic collateral circulation in portal hypertension could be biological, which would allow for a pathophysiological integration of the cardiocirculatory alterations produced in this severe and very common condition.

2. The portal hypertensive inflammatory response

The successive impairments of the ischemia-reperfusion, immunological activation and worsening of angiogenesis phenomena could be integrated as successive phenotypes when portal hypertension exists. Since these phenotypes characterize the inflammatory response, portal hypertension is expressed by the body, either as splanchnic or systemic, with a low-grade inflammatory response [14,15]. The basic pathophysiological mechanisms that control the abovementioned phenotypes, are typical of inflammation and are like those expressed during normal embryonic development. This is why we could suspect that these mechanisms originated long ago [16–19].

Furthermore, we could correlate the phenotypes that characterize inflammation in portal hypertension with the extra- and intra-embryonic functions. Hence, the amniotic functions could be like those produced during portal hypertension after ischemia-reperfusion phenotype expression. In turn, different functions of the innate and acquired immune responses in portal hypertension would reflect typical vitelline sac functions.Lastly, the connective and angiogenic remodelation in portal hypertension seem to represent the embryonic phenomena that occurs after gastrulation is produced. Therefore, the metabolic impairments that are developed in portal hypertension associated with chronic liver injury, which also characterize these three phenomena, would be similar to those of extra-amniotic and vitellin and intra-embryonic development [17,18]. If it is considered that portal hypertension secondary to chronic hepatic insufficiency induces a low-grade inflammatory response during its compensated phase, then it could be deduced that its worsening could provoke an acute-on-chronic inflammatory response when there is hemorrhage, infection or hepatic insufficiency worsening. This worsening of the inflammatory response during the evolution of portal hypertension would explain why ascites appear, as well as hepatorenal failure and hepatic encephalopathy, and why it is called acute-on-chronic liver disease [16–18].

Furthermore, during the compensated stages of portal hypertension, the successive and overlapped expressed phenotypes could be named: ischemia-reperfusion or amniotic phenotype, vitellogenic-like phenotype, and remodeling or gastrulation-like phenotype. The names of these inflammatory phenotypes developed during the compensated stages of the portal hypertension are based on some metabolic similarities that can be established with the abovementioned phases of embryonic development in chronic liver injury [17,18]. However, the decompensation related to the factors that lead to worsening the hepatic insufficiency would induce a high-grade inflammatory response with ascites and hepatorenal syndrome [16–18].

When a low-grade inflammatory response gets worse, the expression of the ischemia-reperfusion phenotype could be more significant because when there are serious metabolic deficits, the low-grade inflammatory response requires less energy through oxidative phosphorylation since its function is mainly carried out by an anaerobic metabolism (Warburg phenomena). In brief, the anaerobic metabolism, since it avoids the Krebs cycle, reduces ATP support to the cellular membrane pumps, and therefore facilitates sodium and water entering the cell. These hydroelectrolitic impairments related to the metabolic deficit would characterize the complications of acute-on-chronic liver disease that is, hydrosaline retention with interstitial edema, ascites, hepatorenal insufficiency and the hepatic encefalophathy [17,19].

This aggravation of the portal inflammatory response involves the return to their initial stages with a hemodynamic decompensation secondary to acute-on-chronic splanchnic ischemia-reperfusion injury, which would result in excessive interstitial edema, overwhelmed lymphatic drainage and excess of lymph collected in the peritoneal cavity with ascites formation [17,19].

In embryonic development, metabolic needs slowly increase, therefore the initial phases could predominate the ischemia-reperfusion phenotype metabolism. The hyperexpression of the ischemia-reperfusion phenotype in the inflammatory response of acute-on-chronic portal hypertension could represent the establishment of those metabolic characteristic alterations of the first phases of embryonic development. If so, the body's objective when faced with a situation that threatens its survival is to try to rebuild itself through primitive embryonic mechanisms. However, this clever survival mechanism takes place without the invaluable metabolic and functional support of a gestating body through the placenta, which a developing embryo has. [20].

A survival mechanism for cirrhotic patients with portal hypertension could be based on the re-expression of embryonic mechanisms with anaerobic metabolism. Aerobic glycolysis associated with this metabolism will allow patients with chronic hepatic insufficiency to survive when the hepatic metabolism is insufficient because oxidative phosphorylation is severely inhibited. However, this embryonic survival mechanism is insufficient because post-natal life does not have the complementary functions that the placenta gives the embryo [20].

Notably, in the production of edema after isquemia-reperfusion in organ transplantation, mediators released by the mast cells, like histamine and serotonin, participate. Thus, amines whose precursors are effectively used in preservation solutions, like histidine and tryptophan, are both components of the preservation solution histidine-tryptophan-ketoglutarate (HTK; Custodiol® [21]. It could be considered that our own body has defensive cellular mechanisms against complications related to ischemia-reperfusion. However, its effectiveness could be reduced in physiological situations, since they would be expressed when an injury, like the hypometabolism, is produced.

3. The fetal-related cardiovascular impairments in portal hypertension

Typical hypertension portal alterations (i.e. splanchnic and systemic vasodilation, portosystemic collateral circulation, high cardiac output, central hypovolemia and low arterial pressure) could represent the same characteristics of embryonic fetal circulation. If so, comprehending the final biological meaning of the alterations associated with portal hypertension could help understand the pathophysiological mechanisms involved in its production. Then, speculating on the hypothetical purpose of the cardiovascular circulatory response to portal hypertension would be justifiable [4,6,7].

Consequently, our theory is based on the clinical similarity of cardiovascular alterations secondary to portal hypertension related to chronic liver disease, with the anatomical cardiovascular characteristics of fetal life. The last objective of the fetal cardiovascular system is to provide the necessary substances required for a physiological development of organs and tissues, until a new cardio-circulatory pattern that will drive the postnatal life of the individual, is established. In brief, fetal circulation is initiated through the umbilical vein, which carries well-oxygenated blood from the placenta. In an early embryonic phase, this well-oxygenated blood from the umbilical vein connects with the vitelline vein. As the *septum transversum* progresses caudally, uniting body walls and splanchnic pleura, the plexus between umbilical and vitelline veins becomes more extensive and is

surrounded by liver parenchyma. The left vitelline vein is small and will soon disappear. The left umbilical vein becomes enlarged, while the right umbilical vein is greatly reduced in caliber and will soon disappear. Then, the uninterrupted capillary liver plexus develops into preferential channels and two left to right anastomoses become prominent: cranially, the *ductus venosus* connects the left umbilical vein to the right vitelline vein; and caudally, the right vitelline vein connects to the left umbilical vein. This latter anastomosis is the future transverse portion of the left trunk of the portal vein [22] (Fig. 1)

In the 4-month fetus, the typical flow pattern of the fetal liver is well established. The left, and only remaining umbilical vein, forms a smoothly curved arch directly continuous with the great *rami portae venae* of the right side. The *ductus venosus* arises at a sharp angle from the great umbilical arch. In turn, the portal vein joins the distal part of this arch smoothly (Fig. 1). The *ductus venosus* drives the oxygenated blood from the umbilical vein to the inferior vena cava, from where it enters into the right *atrium* and, through the oval hole reaches the left *atrium* and, finally, the aorta [22,23].

However, this oxygenated blood is mixed with venous blood of different origins. Thus, the blood, from the inferior limbs, abdomen, and pelvis, is transported through the inferior vena cava to the right *atrium,* where it is mixed with the oxygenated blood from the umbilical vein. Also, the blood of the superior vena cava coming from the head reaches the right ventricle and the pulmonary trunk, bypassing the *interatrium* oval hole. However, since the lungs do not function yet, this blood is diverted by another shunt, the ductus arteriosus Botalli, from the pulmonary trunk to the aorta [23] (Fig. 2).

Therefore, in the *fetus*, the blood in the descending aorta is mixed with venous blood and it must be oxygenated again in the placenta, where it is conducted through the umbilical arteries (Fig. 2). Thus, a reduced degree of oxygen between the venous and arterial circulation, in terms of the postnatal period, is established.

4. The return to a fetal-like circulation induced by portal hypertension

The systemic and splanchnic impairments produced in patients suffering from portal hypertension related to chronic liver disease have some properties that are very similar to those present in the *fetus* circulation. Indeed, as this disease progresses, this similarity becomes more apparent. Moreover, in portal hypertension, the splanchnic venous circulation converging into the portal vein

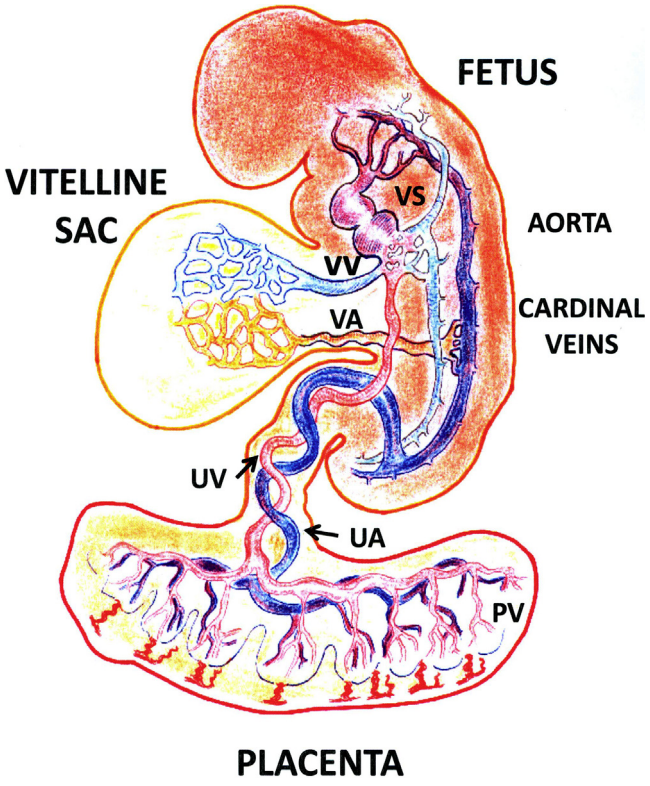

Fig. 1. Schematic representation of the embryonic cardiovascular system. In the vitelline sac and the chorion or primitive placenta, trophism and embryonic-fetal development are successively founded. The venous sinus receives blood from the vitelline sac, the chorion, and the cardinal veins. Blood from the heart passes into the branchial arches through the aortic arches and to the rest of the embryo's body through the aortas. At first there are two, which vascularize the vitelline sac and the embryonic placenta, both which are extraembryonic structures. The umbilical arteries transport deoxygenated fetal blood to the placenta and the umbilical vein brings oxygenated blood to the fetus. One or two placentary truncal vellosities constitute a cotydelon. The endometrial or spiral arteries carry oxygenated blood with nutrients, which flows through the vellosities. After the oxygenated blood exchanges gases and substrates with the fetal blood, the endometrial veins drain it. PV: placental villi; UA: umbilical artery; UV: umbilical vein; Va: vitelline artery; VS: venous sinus; VV: vitelline vein.

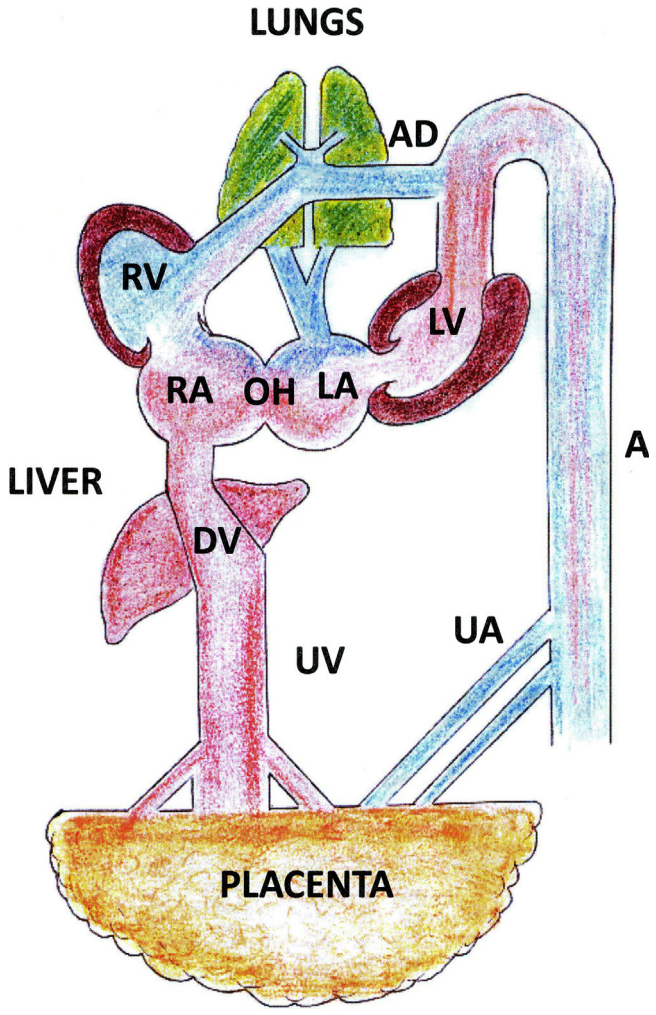

Fig. 2. Schematic representation of the prenatal blood circulation. The blood, oxygenated in the placenta, is transported to the fetus through the umbilical vein, crosses the liver through the Arancio venous duct and reaches the left cardiac cavities and aorta quickly by means of interauricular right-left shunts (oval hole) and pulmonary shunts (ductus arteriosus Botalli). A: Aorta: AD: arterious duct; DV: ductus venous; LA: left *atrium*: LV: left ventricle; OH: oval hole; RA: right *atrium*; RV: right ventricle; UA: umbilical artery; UV: umbilical vein.

seems to acquire characteristics similar to the umbilical venous circulation in the *fetus* since it is arterialized.

Portal hypertension produces vasodilation on the arterial splanchnic bed [13]. This includes the hepatic and superior mesenteric arteries, with hyperdynamic circulation, declined oxygen delivery and nutrients, which limits the free exchange between capillaries and parenchymal cells and the production of pathological angiogenesis in the liver and the gastrointestinal tract [4,6,13,14,24]. Deficits in oxygenation in the splanchnic organs are considered the primary inducer of angiogenesis, either in physiological or in pathological conditions [13,25,26].

In liver cirrhosis, angiogenesis occurs mainly along areas of hypoxia, inflammation and fibrogenesis, and gives rise to intrahepatic shunts that bypass sinusoids and drain blood from the portal to the central *venulae*, suprahepatic veins, and inferior vena cava [3,10]. Vasodilation and angiogenesis are also the cause for the structural impairments present in the gastrointestinal tract. Since the most important structural alteration produced in the gastrointestinal tract is vascular, the convenient name of "hypertensive portal intestinal vasculopathy" has been considered [27].

The underlying mechanisms of the splanchnic hyperdynamic circulation are still unclear. It is considered, however, that the mechanisms implicated in the arterial splanchnic vasodilation depend on the time and the severity of the pathology, with the participation of the different components of perivascular mesenteric innervation in decompensated chronic liver disease rearranged [28–30]. In portal hypertension and liver cirrhosis high hepatic and mesenteric arterial vasodilation and arteriovenous shunting are factors that induce portal vein remodeling, which means the arterialization of the portal venous wall [31].

Furthermore, the increased liver arterial flow causes the sinusoidal arterialization. During the evolution of this condition, there is also a thickening in the basement membrane that leads to a process named "sinusoidal capillarization", in which sinusoidal endothelial cells turn into capillary-type endothelial cells [32] (Fig. 3).

Along the process of arterialization of the portal hypertensive system, the splanchnic venous flow with increased oxygen tension values, quickly reaches the left cardiac cavities and through them, the aorta. Thus, the umbilical vena flow pathway occurring in prenatal development is recreated (Figs. 2 and 3). For this purpose, the patient with portal hypertension progressively establishes porto-systemic collateral circulation and therefore, the portal blood reaches the inferior vena cava (shunts splenorenal and haemorrhoidal) and the superior vena cava (shunt coronary-azygos [1,2,13].

In postnatal life, an interauricular communication does not commonly exist through the oval hole, nor does it exist in the right-left shunt through the ductus arteriosus Botalli. However, in the cirrhotic patient, the portal blood that drains into the right cardiac cavities also reaches the left cardiac cavities and aorta through a pathological pulmonary circulation trying to simulate fetal circulation. That is, a remodelation of the pulmonary circulation is produced, which includes intrapulmonary vascular dilatation, capillary and precapillary dilatation, neo-angiogenesis, and arterio-venous shunting [33,34]. In particular, the existence of intrapulmonary arterio-venous shunts and the dilation of capillaries near the pulmonary alveoli reduce the oxygen diffusion and produces a low arterial oxygen saturation [33,35].

5. The hypothetical reexpression of the prenatal circulation by the cirrhotic patient

The quick circulation of the portal blood through the right cardiac cavities, where it mixes with the venous blood from the superior and inferior vena cava, due to its poor pulmonary oxygenation, induces hypoxemia in the cirrhotic patient and in the fetus aortic blood [36] (Figs. 2 and 3). However, the fetal aortic blood is oxygenated in the placenta where the umbilical arteries reach, whereas in the patient with cirrhotic chronic liver failure, the aortic blood returns to the splanchnic area through the celiac trunk and the mesenteric arteries (Fig. 3).

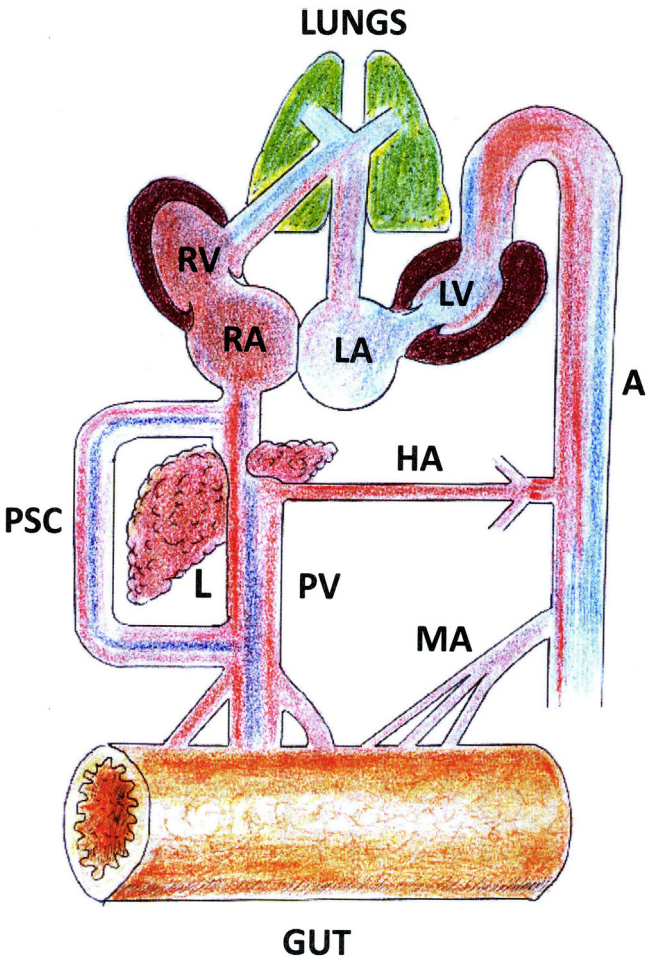

Fig. 3. Schematic representation of the post-natal blood circulation when there are liver cirrhosis and portal hypertension. Portal blood quickly reaches the left cardiac cavities and the aorta through portosystemic collateral vessels, and the right-left intrapulmonary shunts, which are favored by hyperdynamic systemic and splanchnic circulation. As in fetal circulation, the aortic blood is hypoxemic since into the aorta join the poorly oxygenated blood flows from the portal vein, both vena cava and pulmonary veins. HA: hepatic artery; L: liver; LA: left *atrium*; LV: left ventricle; MA: mesenteric arteries; PSC: portosystemic collaterals; PV: portal vein; RA: right *atrium*; RV: right ventricle.

This hypothetical reexpression of the prenatal circulation by the cirrhotic patient, but without the functional placental support, would be the cause of the hypoxemia, dysnea, cyanosis, and finger-clubbing [2,35]. In addition, when this prenatal-like circulatory condition is decompensated, the hypotension related to splanchnic vasodilatation, is aggravated [33,36]. Then, organ failure begins, with the hepatorenal syndrome and ascites standing out. [37,38].

Ascites is the final consequence of the higher decompensated splanchnic lymphatic system. It is accepted that when lymphatic drainage mechanisms are overwhelmed, excess lymph is accumulated in the peritoneal cavity and the result is the development of causing ascites [39–41]. However, ascitic fluid creation is a not well-known pathogenic mechanism. Some of the biochemical characteristics of ascitic fluid make it similar to another bioactive medium, the amniotic fluid [16].

The amniotic fluid that surrounds the fetus may be considered an extension of the extracellular space of the fetus. The functional comparison of amniotic and ascitic fluids would imply that in the decompensated portal hypertensive syndrome, the abdominal mesothelium acquires properties of the amniotic membrane or amnion [17,18]. This hypothesis would imply several suppositions or suggestions. For example, the intestine, in the case of portal hypertensive ascites, could not benefit from the supposed trophic properties of the ascitic fluid given that the peritoneal cavity-gastrointestinal pathway doesn't exist in post-natal life [16–20].

Likewise, when the cirrhotic patient takes on a prenatal-like circulation, the splanchnic arterial circulation is stimulated, so much so that it is equivalent to umbilical arterial circulation and therefore, aims to oxygenate and nourish the body while eliminating harmful metabolized products.

Given that the splanchnic arterial circulation vascularizes abdominal and peritoneal organs together [42], the resulting pathology should be considered as having complementary pathophysiological mechanisms, that is, gut-liver axis- and peritoneal-related ones. If so, the hypotheses that while the peritoneum acquires amniotic properties, the gut-liver axis would therefore express trophoblastic, that is placental, functions. Therefore, as during embryonic development, the extra-embryonic membranes or structures [43] are responsible for the nourishment and development of an emergent trophic deficiency that causes the chronic liver insufficiency. Moreover, when the hepatic cellular differentiation process begins during the fetal development, the incidence of noxious factors, like ischemia, hypoxia, the gestational alloimmune disease or the toxic metabolic hepatopathies would cause hepatomegaly and splenomegaly and ascites, all of them alterations that characterize the chronic liver disease. In these situations, the ascitic fluid reduces the amniotic liquid and induces the development of oligohydramnios [44]. Therefore, the incidence of this compensation mechanism in neonates with hepatic insufficiency would indicate the earliness in which it is stablished

In essence, when a pathology that incapacitates the body for a normal or physiologic function, the processes of cellular dedifferentiation could represent a return to early stages of the development. The different metabolic and nutritional needs that characterize the first phases of the embryologic development when they are established in the adult organism create a pathological situation. However, their objective could be beneficial for the organism. The problem is that today, we don't know how to take advantage of its usefulness to return to normality. Therefore, alpha-fetoprotein elevated serum levels correlates with the degree of malignancy of various liver diseases and tumors, including hepatocarcinoma and, therefore it is associated with a stage of embryologic cellular involution [45]. However, the metabolic and functional usefulness that can be offered to patients is not known yet today.

The functional comparison of the gastrointestinal pathology in the cirrhotic patient with the placental function during fetal development could be based on subtle microcirculatory similarity. The placental nutrient sensing model proposes that the syncytiotrophoblast integrates maternal and fetal signals to regulate placental function. The syncytiotrophoblast, the transporting and hormone producing epithelium of the placenta, is an epithelium with a maternal-facing microvillous plasma membrane and a fetal-facing basal plasma membrane. In this structure, the umbilical arteries carry the deoxygenated fetal blood to the arborescent chorionic villous, where it is oxygenated and receives nutrients from the maternal blood, which comes from the spiral endometrial arteries and flows through the intervillous spaces [23,46].

This placental sense could explain the objective of the portal intestinal "congestive" vasculopathy, which displays villous abnormalities, i.e. congested rounded blunt villi, and vascular lesions. In particular, this vasculopathy is characterized by microcirculatory changes, including inflammatory-like lesions and an exacerbated angiogenesis that produces angiodysplasia-like lesions, small flat red-point lesions, elevated large cherry red spots, angioectasias and varices, associated with a reticulated or mosaic mucosal pattern [47]. In essence, the association of dilated and proliferated vessels that causes small red patches and the tortuously enlarged veins with serpiginous or nodular shape could be microcirculatory traces of the vellosities and the intervillous spaces of the placental cotyledons.

6. Conclusion

In summary, portal hypertension and cirrhosis produce a hyperdynamic systemic and splanchnic circulation. In the current study, a similarity between the pathological circulation in liver diseases and prenatal life is proposed. In brief, a regression to the fetal stages that would impose chronic liver insufficiency and portal hypertension during post-natal life would induce splanchnic macro- and micro-circulatory impairments. The final purpose of these changes would be the re-expression of the functions developed by the extraembryonic, amniotic and trophoblastic structures during prenatal life. The prenatal meaning of pathophysiological mechanisms in cirrhosis would favor translational concepts for their prophylaxis and treatment.

Conflict of interest

We have no Conflict of Interest.

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