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Pregnancy in idiopathic non-cirrhotic portal hypertension: A multicentric study on maternal and fetal management and outcome

Filipe Andrade[1,2], Akash Shukla[3], Christophe Bureau[4], Marco Senzolo[5], Louis D'Alteroche[6], Alexandra Heurgué[7], Juan-Carlos Garcia-Pagan[8], Fanny Turon[8], Frédéric Oberti[9], Dhiraj Tripathi[10], Olivier Roux[1], Pierre-François Ceccaldi[12], Emmanuelle de Raucourt[11], Audrey Payancé[1], Dominique Valla[1,13,15], Aurélie Plessier[1,13], Pierre-Emmanuel Rautou[1,14,15,*], for the VALDIG investigators

[1]*Service d'Hépatologie, DHU Unity, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France;* [2]*Department of Medicine, Hospital Pedro Hispano, Matosinhos, Portugal;* [3]*Department of Gastroenterology, Seth GS Medical College and KEM Hospital, Mumbai, India;* [4]*Service d'Hépato-gastro-entérologie, CHU Toulouse, Toulouse, France;* [5]*Multivisceral Transplant Unit, Department of Surgical and Gastroenterological Sciences, University Hospital of Padua, Padua, Italy;* [6]*Service Hépato-gastro-entérologie, CHU Tours, France;* [7]*Service d'Hépato-Gastro-entérologie, Hôpital Robert-Debré, Reims, France;* [8]*Barcelona Hepatic Hemodynamic Lab and Liver Unit, Hospital Clinic-IDIBAPS and CIBERehd, University of Barcelona, Spain;* [9]*University Hospital of Angers, Department of Hepatology, Angers, France;* [10]*Liver Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK;* [11]*Hôpital Beaujon, Service d'Hématologie Biologique, Clichy, France;* [12]*Service de Gynécologie-Obstétrique, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France;* [13]*INSERM, UMR1149, Centre de Recherche sur l'Inflammation, Paris, France;* [14]*INSERM, U970, Paris Cardiovascular Research Center - PARCC, Paris, France;* [15]*Université Denis Diderot-Paris 7, Sorbonne Paris Cité, 75018, Paris, France*

Background & Aims: A total of 15% of patients with idiopathic non-cirrhotic portal hypertension (INCPH) are women of childbearing age. We aimed to determine maternal and fetal outcome of pregnancies occurring in women with INCPH.

Methods: We retrospectively analyzed the charts of women with INCPH followed in the centers of the VALDIG network, having had ≥1 pregnancy during the follow-up of their liver disease. Data are represented as median (interquartile range).

Results: A total of 24 pregnancies occurred in 16 women within 24 (5–66) months after INCPH diagnosis. Four women had associated partial portal vein thrombosis before pregnancy. At conception, 2 out of the 16 women had detectable ascites and others were asymptomatic. Out of these 24 pregnancies, there were four miscarriages, one ectopic pregnancy, and one medical termination of pregnancy at 20 weeks of gestation. Out of the 18 other pregnancies reaching 20 weeks of gestation (in 14 patients), there were nine preterm and nine term deliveries. All infants were healthy at delivery, but one died at day 1 of unknown cause and one at day 22 of infectious meningitis; both were preterm. Concerning mothers, two had worsening of ascites, two had variceal bleeding despite non-selective betablockers during pregnancy and one developed a main portal vein thrombosis in early postpartum. Genital bleeding occurred in three patients, including two receiving anticoagulation. All 16 women were alive and asymptomatic after a median follow-up of 27 (9–93) months after last delivery.

Conclusion: The overall outcome of women with INCPH who become pregnant is favorable despite a significant incidence of complications related to portal hypertension. Fetal outcome is favorable in most pregnancies reaching 20 weeks of gestation.

Lay summary: About 15% of patients with idiopathic non-cirrhotic portal hypertension are women of childbearing age, who can become pregnant. As available reports on pregnancy in these women are scarce and heterogeneous, it is unclear whether or not pregnancy should be contraindicated in this setting. We provide detailed data showing that, regardless of the associated conditions, the overall outcome of women with idiopathic non-cirrhotic portal hypertension becoming pregnant is good despite a significant incidence of complications related to portal hypertension, and that fetal outcome is favorable in most pregnancies reaching 20 weeks of gestation.

Introduction

Idiopathic portal hypertension, non-cirrhotic portal fibrosis and idiopathic non-cirrhotic portal hypertension (INCPH) indicate the same clinical entity.[1] These terms, thereafter referred to as INCPH, designate a heterogeneous group of liver diseases causing portal hypertension and characterized by the absence of cirrhotic modification of the liver parenchyma and the patency of the portal and hepatic veins. Liver histological lesions found in patients with INCPH include obliterative portal venopathy, hepatoportal sclerosis, nodular regenerative hyperplasia and incomplete septal cirrhosis. The main complications of INCPH include the development of portal vein thrombosis and of gastrointestinal bleeding related to portal hypertension.[2] Although called idiopathic, INCPH has been associated with various conditions including thrombophilia, hematologic malignancies, human immunodeficiency virus infection, genetic and immunological disorders.[2]

Keywords: Preterm; Delivery; Miscarriage; Portal hypertension; Hemorrhage.
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* Corresponding author. Address: Service d'hépatologie, Hôpital Beaujon, 100 boulevard du Général Leclerc, 92100 Clichy, France. Tel.: +33 1 40 87 52 83; fax: +33 1 40 87 55 30.
E-mail address: pierre-emmanuel.rautou@inserm.fr (P.-E. Rautou).

About 15% of patients with INCPH are women of childbearing age, who can become pregnant.[3,4] However, pregnancy and postpartum are prothrombotic states and pregnancy might exacerbate portal hypertension.[5–7] As available reports on pregnancy in women with known INCPH are scarce and heterogeneous, it is unclear whether pregnancy should be contraindicated in this setting.[5]

The current study aimed to assess the maternal and fetal outcome of pregnancies occurring in women with INCPH.

Patients and methods

Definitions

INCPH diagnosis was based on fulfilling all the following criteria: (a) absence of cirrhosis based on histology, and/or on a liver transient elastography value <10 kPa; and (b) one or more signs of portal hypertension among enlarged spleen size, platelet count $<150 \times 10^9$/L, esophageal varices, non-malignant ascites; and (c) no hepatic vein or complete portal vein thrombosis at INCPH diagnosis.

The date of INCPH diagnosis was the date of first identification of signs of portal hypertension.

In order to determine factors influencing the outcome of pregnancy, we identified *a priori* two types of outcome, as previously defined for pregnant women with portal vein thrombosis or Budd-Chiari syndrome.[8,9] Outcome of pregnancy was considered favorable when live birth occurred at 32 or more completed weeks of gestation, with a healthy infant and no serious obstetrical complications. The outcome of pregnancy was defined as unfavorable otherwise (miscarriages or birth before 32 weeks or serious obstetrical complication or serious infant health problem). Very preterm birth was defined as live birth between 20 and 31 completed weeks of gestation, moderately preterm birth between weeks 32 and 36, and term birth as live birth at 37 or more completed weeks of gestation. Miscarriages were defined as a termination of pregnancy before 20 weeks of gestation.[10]

Study group

Between April 2016 and March 2017, we contacted all the centers of the Vascular Liver Disease Interest Group (VALDIG) and of the French network for vascular liver diseases to retrospectively identify all women with INCPH having had ≥1 pregnancy after the diagnosis of their liver disease. When INCPH was diagnosed during pregnancy, this pregnancy was considered for the present study only if liver disease diagnosis occurred during the first trimester of pregnancy in an asymptomatic woman. We excluded pregnancies voluntarily interrupted for non-medical reasons from this analysis. We thus included 16 women having had 24 pregnancies between 2005 and 2017, after INCPH diagnosis: nine pregnancies in six patients from Clichy, France; four pregnancies in two patients from Mumbai, India; three pregnancies in two patients from Toulouse, France; two pregnancies in one patient from Tours, France; two pregnancies in one patient from Reims, France; one pregnancy in one patient from Angers, France; one pregnancy in one patient from Barcelona, Spain; one pregnancy in one patient from Padua, Italy and one pregnancy in one patient from Birmingham, United Kingdom. One of these cases has already been reported in a previous publication.[11]

This study was approved by the Institutional Review Board of Paris North Hospitals, Paris 7 University, AP-HP (N° 16-012). The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Work-up and management

For all patients, a standardized case record form was completed with data extracted from the medical charts. Information was collected on disease course and treatment of INCPH before pregnancy, underlying conditions, and number and outcome of pregnancies.

Statistical analysis

Continuous variables are presented as median (interquartile range), and categorical variables as absolute and relative frequencies. Comparisons between groups of quantitative and qualitative variables were performed using Mann–Whitney and Fisher exact tests, respectively. Data handling and analyses were performed with the Statistical Package for Social Sciences version 24 (SPSS Inc., Chicago, IL).

Results

Patients' characteristics from INCPH diagnosis to conception

Sixteen women had 24 pregnancies after INCPH diagnosis: ten women had one pregnancy, four women had two pregnancies and two had three pregnancies. INCPH was diagnosed during the first trimester of pregnancy in two patients (patients 3 and 8).

Characteristics of these 16 women at INCPH diagnosis are presented (Table 1). Liver function was preserved, since all patients had an international normalized ratio below 1.5 and a serum bilirubin level below 2 mg/dl. Twelve women (75%) had esophageal varices at INCPH diagnosis.

None of the women underwent ovulation induction therapy or medically assisted reproduction. Overall, median duration between diagnosis of INCPH and conception was 24 (5–66) months. During that period, Patient 7 had a transjugular intrahepatic portosystemic shunt (TIPS) placement because of refractory variceal bleeding during a first pregnancy and then had two subsequent pregnancies, as detailed below. One patient (Patient 11) received a TIPS for secondary prophylaxis of variceal bleeding. A surgical portosystemic shunt was performed in another patient because of refractory ascites (Patient 9). However, the shunt subsequently occluded and a TIPS was placed, which was followed by ascites control. This patient developed portopulmonary hypertension, but did not receive any specific treatment prior to pregnancy since mean arterial pressure was 33 mmHg (Patient 9).

At conception, prophylaxis for variceal bleeding (primary in eight pregnancies, secondary in 10 pregnancies) consisted in non-selective betablockers alone in eight pregnancies, betablockers with endoscopic band ligation in five pregnancies, and TIPS in five pregnancies. In six pregnancies, there was no prophylaxis for variceal bleeding, in five cases because there were no or small varices and in one case because of poor compliance to treatment (Patient 8). Two patients interrupted betablockers during pregnancy (Patient 16) or pregnancy and breastfeeding (Patient 2) since they had concerns about potential fetal toxicity (Fig. 1).

At conception, two patients had ascites only detectable at abdominal ultrasonography and no patient had hepatic encephalopathy.

Table 1. Characteristics of the 16 women at INCPH diagnosis.

ID	Age (yr)	Number of pregnancies	INCPH revealed by	Direct signs of portal hypertension		Indirect signs of portal hypertension			Liver histological changes
				Esophageal varices	Other	Platelet count (G/L)	Ascites	Spleen size	
1	17	1	Thrombocytopenia and splenomegaly.	Large	Porto-systemic collaterals at imaging	109	No	19 cm	
2	31	1	Variceal bleeding	Large	Gastro-intestinal bleeding Intrahepatic collateral veins	50	No	18 cm	Hepatoportal sclerosis
3	28	1	Thrombocytopenia and splenomegaly.	Small	–	97	No	16 cm	
4	32	1	Splenomegaly	No	PV enlargement	273	No	16 cm	Perisinusoidal fibrosis
5	36	1	Thrombocytopenia and splenomegaly.	No	–	70	No	18 cm	Sinusoidal dilatation Liver architecture disturbance Portal tract abnormalities
6	35	1	Thrombocytopenia and splenomegaly.	Medium	HVPG: 3 mmHg Porto-systemic collaterals at imaging	35	No	19 cm	Sinusoidal distension Liver architecture disturbance
7	30	3	Variceal bleeding	Medium	Gastro-intestinal bleeding Porto-systemic collaterals at imaging HVPG: 6 mmHg PSG:15 mmHg	70	Yes*	16 cm	NRH
8	21	2	Splenomegaly	Large	Porto-systemic collaterals at imaging HVPG: 18 mmHg	130	No	16 cm	OPV
9	26	1	Ascites	No	HVPG: 19 mmHg	220	Yes	normal	VOD
10	20	1	Liver blood test abnormalities	Medium	–	147	No	normal	Normal liver parenchyma.
11	39	2	Variceal bleeding	Large	Gastro-intestinal bleeding HVPG: 4 mmHg PSG: 15 mmHg at TIPS placement	173	No	n.a.	Perisinusoidal fibrosis Portal tract abnormalities
12	36	2	Pancytopenia	No	Porto-systemic collaterals at imaging	52	No	20 cm	NRH Sinusoidal dilatation
13	24	2	Liver blood test abnormalities	Medium	–	82	No	17 cm	Fibrotic portal tracts Liver architecture disturbance
14	24	1	Ascites	Large	Porto-systemic collaterals at imaging HVPG: 7 mmHg	40	Yes	16 cm	NRH
15	27	3	Variceal bleeding	Large	Gastro-intestinal bleeding	69	Yes*	16 cm	Normal
16	20	1	Ascites	Medium	Porto-systemic collaterals at imaging	100	Yes	20 cm	Portal tract abnormalities

HVPG, hepatic vein pressure gradient; INCPH, idiopathic non-cirrhotic portal hypertension; LS, liver stiffness using Fibroscan; NA, not available; NRH, nodular regenerative hyperplasia; OPV, obliterative portal venopathy; PSG, portosystemic gradient; PV, portal vein; VOD, veno-occlusive disease; *ascites only at abdominal ultrasonography. Esophageal Varices: small: dilated veins (<5 mm) still at level of surrounding tissue; medium: dilated, straight veins (>5 mm) protruding into the esophageal lumen but not obstructing them; large: intense and winding veins already obstructing the esophageal lumen considerably.

Anticoagulation and thrombosis

Before conception, four women had right or left portal branch thrombosis. Three women were not treated with anticoagulation (Patients 7, 11 and 16) and one was receiving vitamin K antagonist (VKA) (Patient 6). In this last patient, VKA was switched to low molecular weight heparin (LMWH) at five weeks of gestation. These four women had seven pregnancies and LMWH was administered since diagnosis of pregnancy in four of these pregnancies (two with prophylactic doses, two with therapeutic doses). None of these four patients had progression of the portal vein thrombosis during pregnancy.

LMWH was also given at prophylactic dose in a patient with a *JAK2*^{V617F} primary myelofibrosis (Patient 4). This patient also received aspirin because of a history of late miscarriage with placental infarction. Both aspirin and LMWH were started at pregnancy diagnosis. In the other 19 pregnancies, no anticoagulation or antiplatelet therapy was given.

Patient 14 developed a partial thrombosis of the main portal vein and of its left and right branches diagnosed 10 days after cesarean section. The patient was asymptomatic, and diagnosis was made by a screening ultrasonography. Treatment with LMWH was introduced and a complete regression of the thrombus was observed by CT-scan six months later.

Gestational course and perinatal complications

Details on the course and outcome of the pregnancies are presented (Table 2). Eight pregnancies were not planned and six were not followed at high-risk obstetrics units. Two women

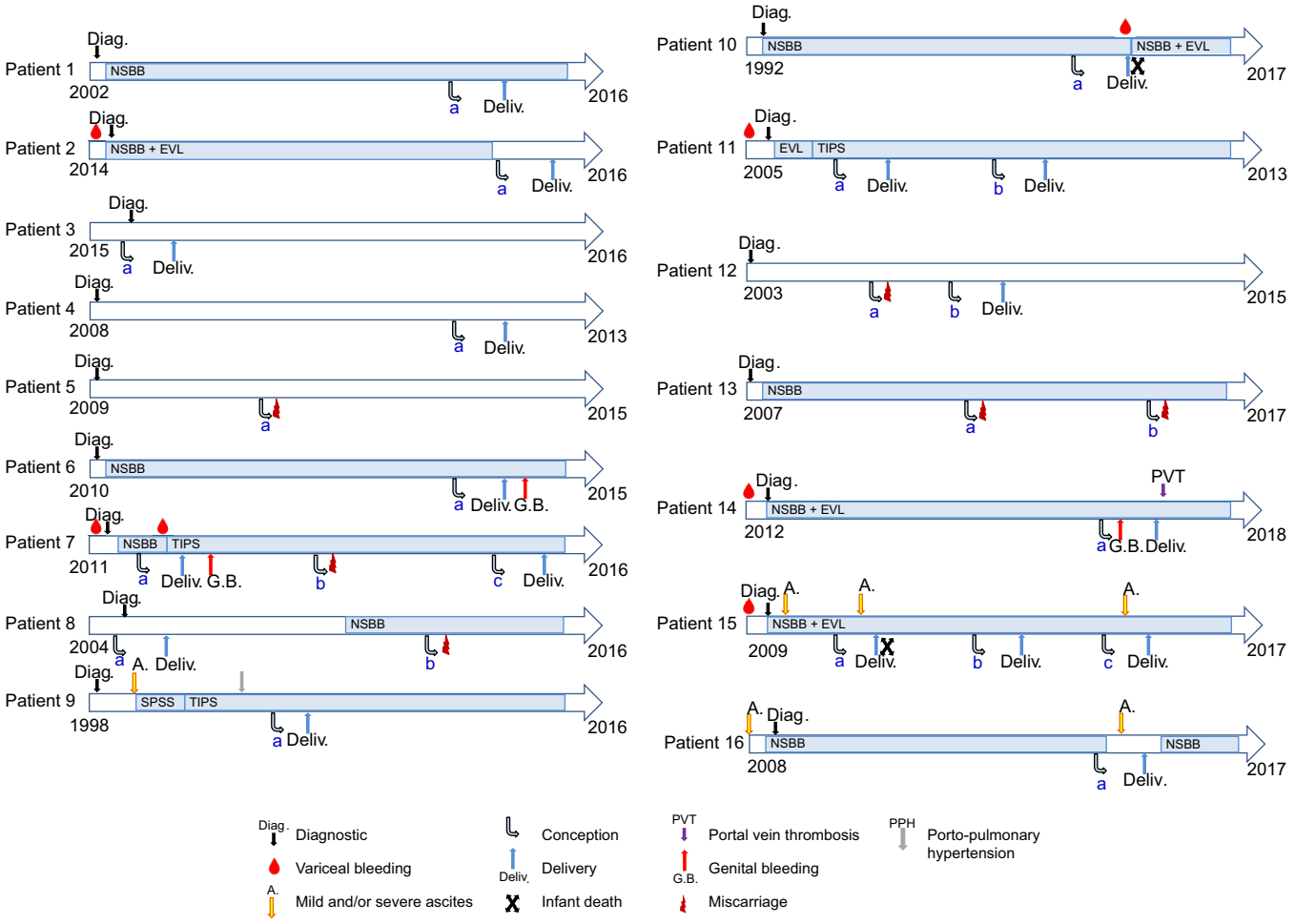

Fig. 1. Outcome of the 24 pregnancies occurring in 16 women with INCPH. Each arrow represents the outcome of a single patient from diagnosis or first symptoms related to INCPH to end of follow-up. Signs above each arrow represent liver disease related events and signs below each arrow represent pregnancy related events. Of note: (A) Patient 2 refused betablockers during pregnancy and breastfeeding; (B) Patient 8 was non-compliant with betablockers during the first years of follow-up despite large oesophageal varices; (B) Patient 9 received a TIPS for refractory ascites and then became pregnant; (D) Patient 16 had medium size varices and was receiving betablockers as a primary prophylaxis for variceal bleeding. She interrupted betablockers during pregnancy because of concerns about potential fetal consequences without endoscopic band ligation. Letters indicate pregnancies. INCPH, idiopathic non-cirrhotic portal hypertension; NSBB, non-selective betablockers; SPSS, surgical portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt. (This figure appears in colour on the web.)

developed gestational diabetes. There was no arterial hypertension or HELLP syndrome.

Median duration of gestation was 35 weeks (22–38 weeks). As shown (Table 3), there was one ectopic pregnancy, four miscarriages and one pregnancy terminated at 20 weeks of gestation for medical reasons due to de prenatal diagnosis of Down syndrome.

Out of the 18 pregnancies reaching 20 weeks of gestation, there was one very preterm birth at 27 weeks of gestation following premature rupture of membranes and chorioamnionitis, eight moderate preterm and nine term deliveries. Out of the 18 deliveries, there were 14 cesarean sections, including two in emergency due to premature rupture of membranes and chorioamnionitis at 37 weeks of gestation and decompensated portopulmonary syndrome, two unplanned due to pathological cardiotocography, six planned due to a history of cesarean section, two planned due to post-term pregnancy and two planned for unspecified reason.

Regarding infants, one Indian baby born at 32 weeks of gestation died at the age of one day from an unknown cause (Patient 15), and one French baby born at 34 weeks of gestation died at the age of 22 days of infectious meningitis (Patient 10). Another baby, born to a mother taking non-selective betablockers, had bradycardia during labor, without sequelae. One infant was small for gestational age (Patient 10, Table 2). All other infants were healthy and had a birth weight appropriate for gestational age.

Two patients with a platelet count below 60×10^9/L at the time of delivery (Patients 6 and 14) received prophylactic platelet transfusion. No other women received platelet transfusion prophylactically.

Three vaginal bleedings occurred, one during pregnancy and two postpartum. Patient 14 had spontaneous severe metrorrhagia at 22 weeks of gestation, requiring transfusion of two red blood cell units. Platelet count was 30 G/L at that time. She then delivered at 27 weeks of gestation. Two postpartum severe vaginal bleedings occurred, both in women with thrombocytopenia and treated with anticoagulation (Table 4): one required transfusion of two red blood cells units and of platelets (Patient 7) and the other patient a uterine artery embolization (Patient 6).

Per the above described definition, pregnancy outcome was classified as favorable in 10 instances (42%), and as unfavorable

Table 2. Course and outcome of the 24 pregnancies.

Patient	Pregnancy number	Planned pregnancy	Follow-up at high risk obstetrics unit	Regular liver imaging	Upper tract GI endoscopy during the 2nd trimester	Delivery	Birth weight classification	Apgar
1	a	Yes	Yes	Yes	No	C	AGA	9
2	a	Yes	No	No	Yes	C	AGA	≥7
3	a	Yes	Yes	Yes	Yes	V	AGA	8
4	a	Yes	Yes	Yes	No	C	AGA	8
5	a	Yes	No	NA	NA	NA	NA	NA
6	a	Yes	Yes	Yes	No	C	AGA	≥7
7	a	No	Yes	Yes	No	C	AGA	≥7
7	b	No	No	NA	NA	NA	NA	NA
7	c	Yes	Yes	Yes	No	V	AGA	≥7
8	a	No	Yes	Yes	Yes	C	AGA	10
8	b	No	No	NA	NA	NA	NA	NA
9	a	Yes	Yes	Yes	No	C – U	AGA	≥7
10	a	No	Yes	Yes	No	C	SGA	10
11	a	Yes	Yes	Yes	No	V	AGA	10
11	b	Yes	Yes	Yes	No	V	AGA	8
12	a	Yes	No	NA	NA	NA	NA	NA
12	b	Yes	No	No	No	C	AGA	10
13	a	Yes	NA	NA	NA	NA	NA	NA
13	b	Yes	NA	NA	NA	NA	NA	NA
14	a	Yes	Yes	Yes	Yes	C - U	AGA	10
15	a	No	Yes	No	Yes	C – U	AGA	9
15	b	No	Yes	No	Yes	C	AGA	9
15	c	No	Yes	No	Yes	C	AGA	9
16	a	Yes	Yes	Yes	No	C – U	AGA	9

AGA, appropriate for gestational age (birth weight between the 10th and 90th percentiles for the infant's gestational age and sex); C, cesarean section; C-U, unplanned cesarean section; GI, gastrointestinal; SGA, small for gestational age (birth weight below the 10th percentile for the infant's gestational age and sex); V, vaginal delivery; NA, not applicable.

Table 3. Gestational course and perinatal complications in 24 pregnancies occurring in women with INCPH.

Weeks' gestation	Number of pregnancies	Mode of delivery	Infant condition
Ectopic pregnancies (13 weeks)	1	–	
<20	4	–	
20–31	2	Caesarean (2)	1 pregnancy termination (Down syndrome), 20 WG (patient 12). 1 healthy, 27 WG (patient 14)
32–36	8	Caesarean (7) Vaginal (1)	6 healthy (patients: 8, 9, 11, 15, 16) 1 died at day 22 with infectious meningitis (patient 10) 1 died at 1 day from unknown cause (patient 15)
≥37	9	Vaginal (3) Caesarean (6)	1 fetal bradycardia (patient 7)

INCPH, idiopathic non-cirrhotic portal hypertension, WG, weeks of gestation.

in 14 cases (58%). No baseline factor was associated with unfavorable outcome (Table 5).

Portal hypertension-related complications

Out of the 24 pregnancies, six complications related to portal hypertension occurred, including two variceal bleedings, three worsening of ascites and one worsening of portopulmonary hypertension. Details on these complications are provided in the supplementary information. Briefly, concerning variceal bleedings, Patient 7 had a first non-severe episode of gastrointestinal bleeding one month prior to conception. At that time, portal branch thrombosis was diagnosed, and non-selective betablockers and LMWH (enoxaparin, 120 mg/day) were started. At nine weeks of gestation, a gastric variceal bleeding occurred. Bleeding was refractory to endoscopic glue and a TIPS was placed leading to bleeding control. Patient 10 had medium size varices at the last endoscopy performed 44 months prior to conception. She was receiving prophylaxis for variceal bleeding during pregnancy with propranolol at a dose of 80 mg/day. No gastrointestinal endoscopy was performed during pregnancy. At 34 weeks of gestation, a variceal bleeding occurred during labor.

Concerning the patient with portopulmonary hypertension (Patient 9), echocardiography surveillance was performed during pregnancy. Pulmonary artery systolic pressure by transthoracic echocardiography reached 120 mmHg with the development of symptoms and echocardiographic signs of hemodynamic compromise. A cesarean section was performed at 33 weeks of gestation. Delivery and the immediate postpartum were uneventful with partial recovery of pulmonary artery systolic pressure. However, three days after delivery, there was a new increase in pulmonary pressures with signs of hemodynamic compromise and acute heart failure. Diuretics and non-invasive ventilation led to a decrease in pulmonary artery systolic pressure to 70 mmHg and to clinical improvement.

No liver-related complication occurred during the other 18 pregnancies, including five pregnancies in three women with TIPS. No woman developed encephalopathy or liver failure.

Table 4. Data in five bleeding episodes during pregnancy or postpartum in women with INCPH.

Patient	Pregnancy number	Age at pregnancy (years)	Anticoagulation during pregnancy	Mode of delivery	Date of bleeding	Bleeding site	Therapy for bleeding
6	a	39	LMWH – therapeutic	Caesarean	Early postpartum	Vaginal	Embolization of uterine artery
7	a	31	LMWH – therapeutic	Caesarean	8 gestation weeks	Gastric varices	Endoscopic treatment and TIPS
7	a	31	LMWH – prophylactic	Caesarean	Early postpartum	Vaginal	Platelets and 2 units of RBC
10	a	35	–	Caesarean	During delivery	Variceal	Endoscopic treatment
14	a	29	–	Caesarean	22 gestation weeks	Vaginal	2 units of RBC

INCPH, idiopathic non-cirrhotic portal hypertension; LMWH, low molecular weight heparin; RBC, red blood cells; TIPS, transjugular intrahepatic portosystemic shunt.

Table 5. Factors associated with pregnancy outcome in 24 pregnancies.

	Favorable outcome (n = 10)	Poor outcome (n = 14)	*p* value
Age at conception – years	34 (28–39)	32 (28–36)	0.52
Duration between INCPH diagnostic and conception (months)	36 (11–60)	44 (27–84)	0.41
Clinical manifestation at INCPH diagnosis			
Ascites	2 (20)	5 (36)	0.36
Spleen size (cm)	16 (10–18)	16 (16–18)	0.54
Esophageal varices	8 (80)	11 (73)	0.67
MELD	10 (8–10)	10 (9–10)	0.76
Platelets count (x10^9/L)	103 (65–173)	70 (65–108)	0.30
Portal vein thrombosis	3 (30)	4 (29)	0.50
Variceal bleeding prophylaxis at conception n (%)			
TIPS	3 (30)	2 (14)	0.33
Beta-blocker	3 (30)	10 (71)	0.06
Antithrombotic therapy during pregnancy			
LMWH	3 (30)	2 (14)	0.33

Data are median (IQR) or frequency (%).
Comparisons between groups of quantitative and qualitative variables were performed using Mann–Whitney and Fisher exact tests as appropriate.
INCPH, idiopathic non-cirrhotic portal hypertension; LMWH, low molecular weight heparin; MELD, model of end-stage liver disease; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.

There was no maternal death and all women were asymptomatic after a median follow-up of 27 (9–93) months after last delivery.

Discussion

INCPH is a rare entity, the awareness of which is increasing, possibly because of the widespread use of non-invasive tests for fibrosis. Indeed, a contrast between low liver stiffness and obvious signs of portal hypertension suggests INCPH, a disease commonly underdiagnosed some years ago.[12] As patients with INCPH usually have a preserved liver function and are asymptomatic, some can become pregnant.[3,4] However, data on pregnancy in women with INCPH were limited and clear conclusions difficult to draw as study populations were heterogeneous, mixing women with liver disease revealed or not by pregnancy, and women with or without extrahepatic portal vein obstruction.[6,13,14] The largest series described the outcome of pregnancies occurring between 1983 and 1998 in 15 Indian women with non-cirrhotic portal fibrosis.[6] However, in 9 out of 15 women, INCPH was revealed by a gastrointestinal bleeding during pregnancy so that these women were not receiving any prophylaxis; moreover, variceal rupture was treated with endoscopic sclerotherapy. Thus, these results cannot be used to base information about the risks of pregnancies for women with INCPH. The present work fills this gap in knowledge, by reporting the outcome of women with INCPH having been pregnant between 2005 and 2017 after diagnosis of their liver disease. Although caution in extrapolation is needed given the limited patient population due to the rarity of INCPH, our main findings are that maternal outcome is good, although liver-related events can occur, and that fetal outcome is relatively favorable when pregnancy reaches 20 weeks of gestation.

The first major finding of the present study is that all 16 women with INCPH becoming pregnant during the follow-up of their liver disease were alive and asymptomatic after a median follow-up of 27 months after last delivery. This finding, together with the absence of mortality reported by Aggarwal and colleagues, indicate that pregnancy should not be contraindicated in women with INCPH.[6] Still, one-third of our patients developed liver-related events, including ascites, variceal bleeding, worsening of portopulmonary hypertension and portal vein thrombosis. Although much caution is needed given the low number of patients, due to the scarcity of INCPH, several practical messages can be drawn from these observations. Firstly, ascites became clinically detectable and required treatment only in the two women having mild ascites prior to conception. Ascites disappeared after delivery. This incidence (2 out of 24 pregnancies) is similar to that in women with portal cavernoma (3 out of 45 pregnancies).[8] Women with mild ascites prior to conception should thus be informed of the risk of worsening of ascites and of the symptoms thereof. Secondly, two variceal bleedings occurred despite prophylaxis with non-selective betablockers. In Patient 7, bleeding can be explained by the absence of secondary endoscopic prophylaxis for variceal bleed-

ing recurrence; indeed, this patient became pregnant only few weeks after a first episode of variceal bleeding. In Patient 10, bleeding happened during labor despite appropriate primary prophylaxis for variceal bleeding. Importantly, the baby died of infectious meningitis at the age of 22 days. This finding is reminiscent of the association of variceal bleeding with a higher incidence of perinatal death observed by Aggarwal and colleagues.[6] Although no similar labor-related variceal bleeding was observed in European women with Budd-Chiari syndrome or portal cavernoma, this case raises the question of a combination of prophylactic band ligation to non-selective beta-adrenergic blockade in women with INCPH and large varices desiring pregnancy.[8,9] Thirdly, one case of worsening of portopulmonary hypertension during pregnancy was encountered. In women with pulmonary hypertension without liver disease, maternal mortality can reach 50%, so that pregnancy is regarded as contraindicated in these women.[15–17] Two pregnancies in women with undiagnosed INCPH and portopulmonary hypertension have been reported, and both women died during puerperium.[18] Portopulmonary hypertension has also been reported to develop during pregnancy in two women with Budd-Chiari syndrome.[19] These data suggest that women with INCPH desiring pregnancy should be questioned about dyspnea and transthoracic echocardiography should be considered before pregnancy for the screening of portopulmonary hypertension. Fourthly, no portal vein thrombosis occurred during the 19 pregnancies without anticoagulation. This suggests that anticoagulation might not be necessary during pregnancy in women without strong risk factors for thrombosis. Ultrasonography might be proposed to those women every three months during pregnancy, given the prothrombotic status of pregnancy. Fifthly, one woman, without known risk factors for thrombosis, developed partial portal vein thrombosis in the early postpartum period. As postpartum is a period of high risk for venous thrombosis and as patients with INCPH are prone to portal vein thrombosis, low molecular weight heparin at a prophylactic dose could be considered for the six weeks after delivery in women not usually receiving anticoagulation.[4,5,20] Moreover, systematic ultrasonography at one, three and six months after delivery could be performed to allow early detection or portal vein thrombosis.

The second major finding in this study was that fetal outcome was favorable in pregnancies reaching 20 weeks of gestation. We observed a rate of pregnancy loss prior to 20 weeks of gestation of 21% (95% CI 5–37%), somewhat higher than the corresponding figure in a healthy female population of similar age and period of observation since an estimated 11%–20% of clinically recognized pregnancies result in spontaneous abortion, but very close to that of women with portal cavernoma (20%, 95% CI 8–32%) and slightly lower than in women with Budd-Chiari syndrome (29%, 95% CI 11–47%).[8,9,21,22] In pregnancies reaching 20 weeks of gestation, the rate of preterm delivery (50%, 95% CI 27–73%) was higher than in the general population in developed countries (5–13%), but infants had no sequelae.[23,24] As compared to other vascular liver diseases, this rate was intermediate between women with portal cavernoma (28%, 95% CI 13–42), and those with Budd-Chiari syndrome (76%, 95% CI 56–97).[8,9] The lower prevalence of thrombophilia in women with INCPH than in those with Budd-Chiari syndrome might account for this difference since some risk factors for thrombosis favor preterm delivery.[25] To what extent liver disease by itself favors preterm birth remains unknown.

Obstetrical bleeding emerged as an important issue, as there were three instances of vaginal bleeding requiring either red blood cell transfusion or embolization. Anticoagulation seems to be associated with a higher risk of bleeding since vaginal bleeding occurred in 2/5 woman receiving anticoagulation *vs.* 1/19 in pregnancies where anticoagulation was not given, but the low power precluded meaningful comparisons. Thrombocytopenia might enhance this risk. Another possible explanation for these vaginal bleedings lies in a high rate of cesarean sections (14 *vs.* 4 vaginal deliveries), much higher than in the general population (14% in Europe).[26] As cesarean section is otherwise known to carry a substantially increased risk of thromboembolic complications and may be hazardous in patients with portal hypertension, it seems safe to recommend vaginal delivery whenever possible, restricting cesarean section to obstetrical indications.[27]

In conclusion, pregnancy should not be contraindicated in women with INCPH with a well-controlled liver disease. These women should however be informed of the risk of liver-related events and of the high rate of miscarriage and preterm birth and be managed by a multidisciplinary team of hepatologists and obstetricians well versed in high-risk pregnancies. Prophylaxis for variceal bleeding should be carefully implemented and band ligation discussed, even as a primary prophylaxis. Portopulmonary hypertension should be searched for prior to conception, since pregnancy can worsen this lung disease. Prophylactic anticoagulation can be considered in the postpartum period to prevent portal vein thrombosis. Cesarean section should be restricted to gynecological indications.

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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
F.A., and P-E.R. wrote the paper. All authors collected the clinical data, discussed and critically revised the manuscript.

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Supplementary data
Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.08.007.

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