



HAL
open science

Maternal and neonatal outcomes and prognostic factors in acute fatty liver of pregnancy

Y. Joueidi, K. Peoc'H, Maela Le Lous, Guillaume Bouzille, Chloé Rousseau, Edouard Bardou-Jacquet, Claude Bendavid, L Damaj, B. Fromenty, Vincent Lavoué, et al.

► **To cite this version:**

Y. Joueidi, K. Peoc'H, Maela Le Lous, Guillaume Bouzille, Chloé Rousseau, et al.. Maternal and neonatal outcomes and prognostic factors in acute fatty liver of pregnancy. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 2020, 252, pp.198-205. 10.1016/j.ejogrb.2020.06.052 . hal-02931946

HAL Id: hal-02931946

<https://hal.science/hal-02931946>

Submitted on 8 Oct 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Maternal and neonatal outcomes and prognostic factors in acute fatty liver of pregnancy

Y Joueidi ^{1*}, K Peoc'h ^{2,3*}, M Le Lous ¹, G Bouzille ⁴, C Rousseau ⁵, E Bardou-Jacquet ^{6,7}, C Bendavid ^{7,8}, L Damaj ⁹, B Fromenty ⁷, V Lavoué ^{1,10}, C Moreau ^{8,10}

¹ Service de Gynécologie obstétrique, Hôpital Sud CHU Rennes, France

² APHP, HUPNVS, UF de Biochimie Clinique, Hôpital Beaujon, F-91118, Clichy, France

³ Université de Paris, UFR de Médecine Xavier Bichat Centre de Recherche sur l'Inflammation (CRI), F-75018 Paris, France.

⁴ PMSI, Hôpital Pontchaillou CHU Rennes, 2 rue Henri Le Guilloux, 35000 Rennes, France.

⁵ Service de recherche clinique, Hôpital Pontchaillou CHU Rennes, 2 rue Henri Le Guilloux, 35000 Rennes, France.

⁶ Service d'Hépatologie, Hôpital Pontchaillou CHU Rennes, 2 rue Henri Le Guilloux, 35000 Rennes, France.

⁷ Univ Rennes, INSERM, INRA, Institut NuMeCan, CHU Rennes, France

⁸ Laboratoire de Biochimie-Toxicologie, Hôpital Pontchaillou CHU Rennes, 2 rue Henri Le Guilloux, 35000 Rennes, France.

⁹ Service de Pédiatrie, Hôpital Sud, CHU Rennes Boulevard de Bulgarie, 35000 Rennes, France

¹⁰ Univ Rennes, CHU Rennes, INSERM, EHESP, IRSET (Institut de Recherche en Santé, Environnement et Travail) UMR_S 1085, F-35000 Rennes, France

*The two first authors collaborated equally to work.

Corresponding author

Dr. Caroline Moreau

Laboratoire de Biochimie-Toxicologie

Hôpital Pontchaillou – CHU Rennes

2, rue Henri Le Guilloux

35033 Rennes Cedex

Tel: 0033299284275

Mail: caroline.moreau@chu-rennes.fr

6030 words

ABSTRACT

Objective: To report complications of Acute Fatty Liver of pregnancy (AFLP), a rare liver disease of pregnancy, and identify prognostic factors for mothers and children.

Study Design: We conducted a retrospective descriptive study over 18 years in three French maternities. Demographic, clinical, biological data, and outcomes of patients and their infants were reviewed.

Results: 142,450 pregnancies from centers were studied. Eighteen patients with AFLP were identified. The prevalence of AFLP was estimated as 1/7,914 pregnancies. Prolonged prothrombin time was identified as a risk factor of maternal complications (OR=0.86, p=0.0493). Gestational age at delivery was the only risk factor associated with fetal or neonate complications (OR=0.37, p=0.0417). One boy died of previously undiagnosed β -oxidation deficiency at eight months.

Conclusion: In AFLP, prothrombin time must be carefully monitored to anticipate major maternal complications. Infants born to mothers with ALFP should be screened as early as possible for mitochondrial fatty acid oxidation deficiency.

Keywords: acute fatty liver of pregnancy, Swansea criteria, metabolic disease, liver, delivery, fetal and maternal outcomes

INTRODUCTION

1
2 The prevalence of liver diseases in pregnancy is estimated at near 3% of all pregnancies in
3 developed countries[1], including liver diseases induced by pregnancy or those revealed
4 during pregnancy. Five liver disorders are specific to pregnancy: *hyperemesis gravidarum*,
5 intrahepatic cholestasis, liver disorders associated with pre-eclampsia (PE), Hemolysis,
6 Elevated Liver enzymes, and Low Platelet count syndrome (HELLP), and Acute Fatty Liver
7 of pregnancy (AFLP). AFLP, initially described in 1940 [2], typically occurs during the third
8 trimester of pregnancy, with an incidence ranging between 1/5,000 and 1/20,000 pregnancies
9 [3–6]. This disease combines non-specific symptoms as nausea, vomiting or headache, and
10 laboratory findings, including elevated transaminases, coagulopathy, and renal impairment.
11 Because of these nonspecific characteristics, there is a lack of international consensus for the
12 diagnosis of AFLP. Several international teams previously proposed criteria, as Ch'ng and al.
13 with Swansea criteria, including both clinical and biological data [7–9] to help with the
14 diagnosis.

15
16 Early delivery remains part of the treatment of this disease. Indeed, current data suggest that
17 the maternal liver recovers quickly after the birth of the fetus[10,11].

18
19 However, the pathophysiology of AFLP remains unclear. Different investigations point to
20 severe mitochondrial dysfunction in the liver [12] and the association of fetal fatty acid
21 oxidation defects with maternal liver disease [8], which could be triggered by several genetic
22 and acquired factors [9]. Long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD)
23 deficiency would play a role in some cases of AFLP [4,13–16]. We conducted a multicenter
24 retrospective study over 18 years to report maternal and perinatal outcomes of AFLP, and
25 identify prognostic factors for mothers and children.

METHODS

Design

1
2 We performed a multicenter retrospective study between January 2000 to July 2018 in three
3
4 maternity centers of the west of France: Rennes, Vannes, and Saint-Brieuc. We performed
5
6 data mining on the program of the medicalization of information systems (PMIS), using the
7
8 following research criteria "liver diseases during pregnancy, childbirth, and puerperium,"
9
10 "acute and subacute liver failure" and "fatty degeneration of the liver not elsewhere
11
12 classified." Approval for the study was obtained from a local institutional review board.
13
14
15

Patients

16
17
18 For the analysis of outcomes and features, we included all patients with a diagnosis of AFLP
19
20 based on the declaration of the clinician in charge of the patient and/or declared within the
21
22 PMIS. A study investigator (YJ) reviewed the clinical, biological, imaging, and pathological
23
24 data for each patient.
25
26
27

28
29 AFLP was defined by the association of clinical, biological and imaging characteristics, after
30
31 the exclusion of any other liver disease of pregnancy as intrahepatic cholestasis of pregnancy,
32
33 toxic or viral hepatitis, HELLP syndrome, PE, or pre-existing liver disease. Diagnosis of
34
35 AFLP was retained if alternative diagnosis could not be made. All patients with diagnosed
36
37 AFLP were included regardless of gestational age or kind of pregnancy (singleton or multiple
38
39 pregnancy).
40
41
42

Data collection

43
44
45 Maternal data included: age at diagnosis, parity, gravidity, consanguinity, ethnicity, medical
46
47 antecedents (hypertension, diabetes, hypercholesterolemia, preexisting liver disease),
48
49 obstetrical history (cholestasis, AFLP, PE, HELLP, cicatricial uterus), body mass index
50
51 (BMI) and mode of delivery. Maternal laboratory data included: aspartate aminotransferase
52
53 (ASAT), alanine aminotransferase (ALAT), creatinine, blood urea nitrogen (BUN), estimated
54
55 glomerular filtration rate (eGFR), serum and urine total proteins, alkaline phosphatase (ALP),
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

gamma-glutamyl transferase (GGT), whole and conjugated bilirubin, bile acid, lactate dehydrogenase (LDH), uric acid, haptoglobin, glycemia, hemoglobin, platelets, leukocytes, prothrombin time (PT), fibrinogen, factor V, and hepatitis serology. Medical imaging data included ultrasounds and computerized tomography. Pathological data concerned LB results and placenta examination. Data collected for the infants included birth weight, Apgar score, sex, pH and lactate at birth, and molecular diagnosis of LCHAD deficiency. We recorded maternal and fetal complications and their outcomes.

Outcome measures

Our primary outcome for mothers was a serious maternal complication: ICU hospitalization, long stay in ICU, disseminated intravascular coagulation (DIC), pleural effusion, ascites, hemorrhage, and/or acute kidney injury.

The primary outcome for the fetuses or neonates was intrauterine death (IUD) and admission to the neonatal intensive care unit (NICU).

Statistical analysis

A descriptive statistical analysis was performed on SAS software (v 9.4). Qualitative data were expressed in number (n) and percentage (%); the quantitative variables were described as follows: N, the minimum and maximum values, medians, and interquartile (IQ) ranges. We considered variables with a p-value lower than 0.05 as significant in univariate analysis.

Univariate logistic regressions were performed on each variable to examine the association between clinical, biological, imaging, and pathology data adverse maternal and neonatal outcomes. For this latter analysis, twin-pregnancies were excluded.

For logistic regression, the severity criteria in the mothers included in the model were: DIC, pleural effusion/ascites, hemorrhage, and malignant hypertension, and severity criteria for the fetuses or neonates included were IUD and NICU admission.

RESULTS

Description of the population

A total of 142,450 pregnancies were recorded in the regional center's neonatal screening registry (covering the three French maternity centers cited above) between January 2000 and July 2018. After exclusion, we identified 122 records of pregnancies using the criteria mentioned previously for AFLP inclusion. One hundred and four women were excluded as they suffered from other pre-existing liver diseases or liver disease of pregnancy that was not AFLP, or because of a lack of final diagnosis (**Figure 1**). Eighteen patients were finally diagnosed as suffering from AFLP, giving an estimated prevalence of 1 case per 7,914 pregnancies. Eleven patients (61%) were primiparous. It was the first pregnancy for nine of them (50%). The mean maternal age at diagnosis was 28.2 ± 4.7 years (17-39 years). One mother had a clinical history of intrahepatic cholestasis of pregnancy (5.6%). None of the patients had major medical or surgical event before the pregnancy. The median BMI was 21.5 kg/m² (IQ: 20.3-24.9; n=15), and three presented a BMI < 19 kg/m² (20%). One of the pregnancies was a spontaneous bichorial twin pregnancy (5.6%). The median gestational age at diagnosis was 35.2 weeks of gestation (WG) (IQ 33.1-37.9). Ten neonates were male (52.6%).

Initial presentation and Swansea criteria in mothers

Clinical, biological characteristics and Swansea criteria are summarized in **Table 1**.

Sixteen patients (89%) experienced prodromal syndrome: nausea and vomiting (61%), abdominal pain (33%), polyuria-polydipsia syndrome (39%), and encephalopathy (22%). Other symptoms at diagnosis included severe asthenia (72%), jaundice (56%), anorexia (28%), episodes of confusion (22%), and skin pruritus (17%).

The biological results are detailed in **Table 2**. Hypoglycemia was reported for six patients. All patients presented hepatic cytolysis with ALAT > ASAT in 11 patients out of 18. All patients

1 had bilirubin higher than 14 $\mu\text{mol/L}$. Low concentrations of fibrinogen were observed in 82 %
2 (reference values: 3.7 to 6.2 g/L in the third trimester of pregnancy). A prolonged
3
4 prothrombin time (PT) was observed in 15 patients (Range: 18-96%). Fourteen patients (78%)
5
6 exhibited an acute kidney injury with a creatinine higher than 100 $\mu\text{mol/L}$ and 50% of patients
7
8
9 > 150 $\mu\text{mol/L}$.

10
11 The leukocytes counts were higher than 11 G/L in 15 of the patients (83%). Overall, 100% of
12
13 the patients presented elevated transaminase and bilirubin levels.

14
15
16 Liver ultrasound was performed in fourteen of the 18 patients (78%). Nine out of the 14
17
18 patients with hepatic imaging data (64%) presented a hyperechoic liver compatible with
19
20 hepatic steatosis without dilatation of bile ducts. Three patients (20%) had ascites.

21
22
23 A LB was performed in three patients (17%) demonstrating, in each case, the presence of
24
25 microvesicular steatosis.

26
27
28 The number of Swansea criteria ranged between 4 and 10. Sixteen patients presented six or
29
30 more Swansea criteria.

31 32 33 Deliveries

34
35
36 The vaginal delivery rate was 11% (two patients in labor at admission, fast labor). All births
37
38 occurred within 48 hours after the admission. In three cases, corticoid fetal pulmonary
39
40 maturation was performed before delivery. In one patient, the diagnosis of AFLP was not
41
42 evident on the day of hospitalization and was made after clinical and biological monitoring.

43 44 45 Maternal Outcomes

46
47
48 The maternal outcomes are summarized in **Table 3**. Fourteen mothers (78%) were
49
50 hospitalized in the ICU for an average length of stay of 2.2 ± 2.2 days (1 to 8 days). Severe
51
52 complications were: DIC (33%), pleural effusion/ascites (17%), acute kidney failure (78%) or
53
54 hemorrhage (17%), including retroperitoneal hematoma, cataclysmic hemorrhage, and
55
56 hemoperitoneum requiring surgical revision. No maternal death was reported, and no mothers
57
58
59
60
61
62
63
64
65

1 needed dialysis or liver transplantation. Trouble of coagulation were not systematically
2 associated with the severity of the hepatic cytolysis.
3

4 Univariate analysis identified that an abnormal PT was associated with severe maternal
5 complications (OR = 0.86 [CI95% 0.73; 1.00] p=0.0493) (**Table 4**).
6

7 Fetal and infant outcomes 8

9
10 The neonatal outcomes are summarized in **Table 3**. Thirteen children (68.4%) were born
11 prematurely, five of them (38.5%) before 34 WG, and eight (61.5%) between 34 and 37 WG.
12 The median birth weight of the neonates was 2,415 g (IQ: 2,015-2,790). Birth weight of less
13 than 2,000 g was observed in 21% of neonates. One suffered from fetal growth restriction
14 (<10th percentile). Ten children (52.6%) were hospitalized in the NICU. Two fetuses died *in*
15 *utero*. In both cases, an emergency cesarean section was performed because of a maternal
16 multi-organ failure. No neonate died during the first care, and one infant died at eight months.
17 Severe complications in the neonates were associated with an early gestational age at delivery
18 (OR = 0.37 [CI95% 0.14; 0.96] p=0.0417) (**Table 4**). The frequency of complications
19 decreased as the gestational age at delivery increased.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35

36 Outcome after the acute episode 37

38 Maternal biological data normalized within the month following delivery without any organic
39 sequelae for mothers.
40

41 All neonates displayed initial healthy development. At eight months, one infant presented
42 with episodes of ocular revulsion, limb hypertonicity, and axial hypotonia secondary to
43 prolonged fasting as part of an infection. The child died of cardiorespiratory arrest with
44 hepatic encephalopathy and hypertrophic cardiomyopathy. LCHAD deficiency caused by a
45 mutation in *HADHA* gene was identified in this child . The only other child screened for
46 *HADHA* mutation did not exhibit any variant.
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

DISCUSSION

1
2 AFLP is a rare but life-threatening complication occurring typically during the third trimester
3
4 of pregnancy. In our cohort, eighteen mothers with AFLP were identified over a 18 years
5
6 period, giving an estimated prevalence of one case for 7,914 pregnancies, similar to that of
7
8 previous studies [17] (**Table 5**).
9

10
11 Diagnosis of AFLP is commonly based on the Swansea criteria, or on the AFLP-Triad
12
13 described by Vigil-De Gracia [7,11,17–20]. In our population, 16 patients exhibited from six
14
15 to ten Swansea criteria. For the two mothers with less than six criteria, HELLP syndrome or
16
17 other liver diseases were rejected. Indeed, in previous cohorts, a small percentage of *bona fide*
18
19 cases of AFLP did not fulfill the Swansea criteria [17,21]. Fifteen mothers exhibited
20
21 prolonged PT, all exhibited elevated transaminases (>46 IU/L), and bilirubin (>14 $\mu\text{mol/L}$)
22
23 that should be considered as arguments for the diagnosis.
24
25
26
27

28
29 Hyperechogenicity of the liver on liver ultrasound scans that we observed in 64% of the
30
31 patients is an additional argument for diagnosis [22–24].
32

33
34 Timely fetal extraction is mandatory to improve both maternal and fetal prognosis [10,25].
35

36
37 There is no consensus for the way of delivery, but cesarean section is associated with lower
38
39 risk of peripartum mortality in this context.
40

41
42 In our cohort, two fetuses (10.5%) died *in utero*, which is in the range of previously described
43
44 fetal mortality [14,15,26]. Gestational age at delivery was identified as the only risk factor
45
46 associated with fetal or neonatal complications (OR=0.37). Early gestational age at diagnosis
47
48 was correlated with more neonatal complications. This factor was previously identified in a
49
50 Chinese cohort as a factor of perinatal death [22]. It remains to be established whether this
51
52 observation is relative to AFLP or secondary to complications of prematurity.
53
54

55
56 To date, maternal mortality in AFLP is estimated at around 2% [7,10,27]. We observed no
57
58 maternal death in our cohort. We identify that prolonged PT was significantly associated with
59
60

1 a risk of severe maternal complications (OR = 0.86). This defect in the coagulation pathway is
2 likely due to the hepatocellular deficiency related to the primary injury of the liver, and
3
4 possibly to the accumulation of some long-chain hydroxy-fatty acids [16]. A deficiency of
5
6
7 coagulation proteins has been previously identified as a risk factor of severe complications in
8
9
10 AFLP [22,28,29]. Zhang *et al.* and Gao *et al.* also observed an association between PT and
11
12 maternal complications in AFLP [22,30].

13
14 In our population, an 8-month old boy died of LCHAD deficiency. LCHAD deficiency
15
16 (OMIM 609016) has previously been reported in children born from mothers suffering from
17
18 AFLP [4,14,16,31]. However, the incidence of LCHAD deficiency is 1/100,000, which is
19
20
21 lower than AFLP. The etiology of AFLP is probably multifactorial, involving maternal and
22
23
24 fetal factors (BMI < 20 kg/m², primiparity [32], multiple pregnancies [19,28,33], male fetus
25
26 [17,34,35], history of AFLP [36]), and genetic and non-genetic factors altering mitochondrial
27
28
29 function [21,37–41]. Infants born from mothers with AFLP should be systematically screened
30
31 for mitochondrial fatty-acid oxidation deficiency to prevent metabolic decompensation.

32
33
34 Our study has several strengths. This study is the most extensive retrospective European study
35
36 on AFLP in the last decade. It provided detailed information on clinical and biological
37
38 characteristics of patients with AFLP. It also gave reports on maternal and fetal prognosis.

39
40
41 However, it is a retrospective study, and the results might not be generalizable. The limited
42
43
44 number of patients reflects the low prevalence of the disease. Two patients did not present six
45
46 Swansea criteria, but were classified as AFLP after the exclusion of all other liver diseases of
47
48 pregnancy. Finally, only two out of 18 children were screened for fatty acid oxidation
49
50
51 disorders and only one of them before clinical decompensation. Association between fatty
52
53
54 acid oxidation disorders and AFLP has been widely reported and, therefore, should have
55
56 triggered neonatal testing in all cases. However, as some contributors to the manuscript are
57
58
59
60
61
62
63
64
65

1 regional referents following all LCHAD deficiency-diagnosed infants in the geographic area,
2 we note that, unfortunately, many children are not tested.
3

4 In conclusion, we identified a prevalence of 1/7,914 pregnancies of AFLP. Prolonged
5 maternal PT was associated with maternal complications. The term at birth correlated with
6 infant complications. Moreover, we point out the need for screening infants for mitochondrial
7 beta-oxidation of fatty acid disorders to limit the risk of infant deaths, when the mother
8 developed AFPL during pregnancy.
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

TABLE LEGENDS

Table 1: Swansea criteria. [7], and clinical signs at diagnosis of AFLP. Criteria were divided into four different classes, namely clinical, biological, imaging, and pathology. Other symptoms were listed below. NA: not available.

Table 2: Biological data at diagnosis for women

Table 3: Patients outcomes and treatments

DIC: disseminated intravascular coagulopathy

Acute kidney failure: Creatinine > 100 $\mu\text{mol/L}$

Hepatocellular insufficiency : cytolysis > 2N, bilirubin > 14 $\mu\text{mol/L}$, PT < 70 % and Factor 5 < 70 %

Table 4: Univariate analysis of the risk factors of severe complications in AFLP (maternal and neonatal)

All variables with a p-value < 0.10 are presented. For this analysis, the mother with twin gestation was excluded, so 17 pregnancies were studied. In bold, are indicated *p* values < 0.05.

Table 5: Primary published studies on AFLP cohorts over the last decade

DIC: disseminated intravascular coagulopathy

FIGURE LEGENDS

Figure 1: Flow chart of patients' selection

We retrospectively selected 122 records in the PMSI database. Among these, 104 patients were excluded as they suffered either from another pre-existing liver disease or from a liver disease in pregnancy that was not AFLP. Moreover, 23 patients with no final diagnosis were excluded. Finally, 18 patients were retained as suffering from AFLP.

1 **DISCLOSURE OF ANY SOURCE OF FINANCIAL SUPPORT OF THE STUDY:** The
2 authors have no disclosures to declare. We did not get any funding for this project.

3 **SHORT TITLE: Prognosis factors in acute fatty liver of pregnancy**
4

5
6 **ACKNOWLEDGMENTS**

7 The authors are grateful to all the physicians and biologists involved in the data collection.
8
9

10
11 **AUTHOR CONTRIBUTIONS**

12
13 YJ, KP, CM designed and performed the research, analyzed the data, wrote and revised the
14 manuscript. ML, GB, CR, EP, EB-J, CB, BF, VL analyzed the data and revised the
15 manuscript.
16
17
18
19
20
21
22

23 **PRÉCIS :** In acute fatty liver of pregnancy, maternal and infant outcomes are associated with
24
25
26 prothrombin time and weeks of gestation at delivery, respectively.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Table 1

Signs	Number of patients with the corresponding criteria	Number of patients with available data
Swansea criteria		
<i>Clinical symptoms</i>		
Nausea and vomiting	11	18
Upper abdominal pain	6	18
Polyuria/polydipsia	7	18
Encephalopathy	4	18
<i>Biological exams</i>		
Elevated bilirubin (> 14 µmol/L)	18	18
Hypoglycemia (< 4 mmol/L)	6	18
Elevated urate (> 340 µmol/L)	13	18
Leukocytosis (> 11 10 ⁹ /L)	15	18
Elevated transaminases (ASAT or ALAT > 42 U/L)	18	18
Elevated ammonia (> 47 µmol/L)	NA	NA
Elevated creatinine (> 100 µmol/L)	14	18
PT<80%	15	18
<i>Imaging and pathological findings</i>		
Ascites or bright liver on ultrasound scan	12	15
Liver biopsy	3	18
Microvesicular steatosis on LB	3	3
Other clinical signs		
Asthenia	13	18
Jaundice	10	18
Skin pruritus	3	18
Anorexia	5	18
Edema	2	18
Hypertension	1	18
Epistaxis	1	18
Metrorrhagia	1	18
Hematemesis	1	18

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Accepted manuscript

Table 2

	Min-max	Median (IQ)	Reference values for third trimester of pregnancy
<i>Hematological data</i>			
Hemoglobin (g/dL)	10.8-16.9	13.2 (IQ 12.4-15.1)	11-12
Leukocytes (10 ⁹ /L)	7.6-26.3	14.9 (IQ 11.9-21)	4-15
Platelets (10 ⁹ /L)	44-347	175 (IQ 154 -227)	150-400
PT (%)	18-97	44 .5 (IQ 31-62)	80-100
Fibrinogen (g/L)	0.57-6.34	2.3 (IQ 1.8-2.86)	5-6
Factor V (%)	21-69	43 (IQ 27-49)	70-120
<i>Biochemical data</i>			
AST (U/L)	96-3486	438 (IQ 236-488)	0-35
ALT (U/L)	124-2148	463 (IQ 290-540)	0-35
Alkaline phosphatase (U/L)	106-1302	340 (IQ 236-595)	30-120
Gamma-glutamyl transpeptidase (U/L)	20-398	74 (IQ 51-231)	0-30
Total bilirubin (µmol/L)	26-206	67.5 (IQ 51-95)	2-12
Lactate dehydrogenase (U/L)	341-2680	824 (IQ 532-1092)	50-150
Creatinine (µmol/L)	41-280	150 (IQ 102-180)	35-71
Glomerular filtration rate (mL/min)	16-137	40 (IQ 33-66)	
Uric acid (µmol/L)	241-1197	578 (IQ 398-607)	120-420

Table 3

Maternal clinical features (n=18)	
Hospitalization in ICU	14 (78%)
Less than two days	9 (72%)
Two days or more	5 (28%)
Hemorrhage	3 (17%)
DIC	6 (33%)
Pleural effusion and or ascites	3 (17%)
Kidney failure	14 (78%)
Hepatocellular insufficiency	18 (100%)
Blood transfusion	6 (33%)
Plasma transfusion	8 (44%)
Fibrinogen transfusion	6 (33%)
Albumin transfusion	2 (11%)
Neonatal outcomes (n=19)	
< 34 WG	5 (26%)
34 - 37 WG	8 (42%)
Intrauterine fetal distress	7 (37%)
Neonatal intensive care unit	10 (53%)
Birth weight < 2,000g	4 (21%)
Fetal death	2 (10.5%)
Infant death from complications	1 (5%)

Table 4

Maternal outcomes				
	Number of cases with the corresponding criterion	Number of patients with severe complications	OR IC 95%	p
Swansea criteria	17	7	2.35 [0.92 ; 6.01]	p = 0.0733
Parity				
0	10	2	10.00 [1.05 ; 95.46]	p = 0.0455
1 or 2	7	5		
PT	17	7	0.86 [0.73 ; 1.00]	p = 0.0493
Neonatal outcomes				
	Number of cases with the corresponding criterion	Number of patients with severe complications	OR IC 95%	p
Gamma-glutamyl transpeptidase	17	10	0.99 [0.98 ; 1.00]	p = 0.0944
Uric acid	13	7	1.01 [1.00 ; 1.03]	p = 0.0635
Gestational age at delivery	17	10	0.37 [0.14 ; 0.96]	p = 0.0417

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Table 5

Reference	Nature of the study	Objectives	number of inclusion	number of AFLP	Diagnosis of AFPL	WG at diagnosis mean +/- SD (wk)	Main results
Lin <i>et al.</i> [42]	8-year retrospective and single-center	To analyze characteristics, outcomes and possible risk factors among obstetrics patients admitted to the ICU	426 pregnant women ≥ 20 weeks of gestational age	5	NA	NA	Pregnancy with acute fatty liver is a risk factor for IUC admission (OR=16.233) Acute fatty liver was statistically significant with pregnant women mortality ($p < 0.05$)
Gao <i>et al.</i> [30]	5-year retrospective and multicenter	To summarize clinical characteristics, outcomes and risk factors of maternal and fetal mortality	140	133	Clinical features and laboratory findings and ≥ 6 Swansea criteria	36.1 \pm 2.7	Maternal death: 68.2% 50% of perinatal death Risk for poor maternal outcomes: male fetus, postpartum diagnosis of AFLP, intrauterine fetal death, DIC, prolonged PT and activated partial thromboplastin time Risk factors for fetal mortality: fetal distress, prolonged activated partial thromboplastin time
Zhang <i>et al.</i> [22]	5-year retrospective study	To collect information from AFLP patients to provide references for future clinical practice	56	56	Based on Swansea criteria and AFPL-triad of Vigil-de-Garcia and Montufar-Rueda	33.68 \pm 4.15	Risk factors for complications: PT and INR Risk factors for perinatal death: Gestational age at delivery, direct bilirubin, and fibrin degradation products Main maternal complications: hypoproteinemia, coagulopathy, acute renal failure, ascites and DIC 16% of perinatal death
Allen <i>et al.</i> [43]	14-year retrospective and multicenter	To determine the incidence of liver diseases in pregnancy, the maternal and fetal outcomes, the long term prognosis	35,101 pregnancies 247 women with liver disease of pregnancy	1	Clinical and biological diagnosis	NA	The infant of the AFLP mother died

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Reference	Nature of the study	Objectives	number of inclusion	number of AFLP	Diagnosis of AFPL	WG at diagnosis mean +/- SD (wk)	Main results
Nelson <i>et al.</i> [6]	38-year retrospective and single-center	To provide a description of clinical and laboratory findings in women with AFLP	492,000 deliveries	51	Clinical and biological diagnosis Swansea criteria and AFPL-triad of Vigil-de-Garcia and Montufar-Rueda	37.0 ± 2.6	Risk factors for complications of AFLP: Hepatic failure with multiorgan involvement Maternal death: 4% Perinatal mortality rate 12% Incidence of 1/10,000 births
Vigil-de Gracia <i>et al.</i> [11]	14-year retrospective and multicenter	To report experience with the diagnostic, the clinical and biochemical findings, complications and maternal-perinatal outcomes	35	35	Clinical symptoms, complications, and laboratory evidence of acute hepatic dysfunction in the third trimester of pregnancy with complete resolution of the liver function postpartum	36	Maternal mortality: 11.4% Fetal mortality rate: 12.5%
Dekker <i>et al.</i> [44]	23-year retrospective and multicenter	To assess maternal death	4,608,253 live births 538 cases of maternal death	6	Clinical and biological diagnosis Microscopic examination of liver in post mortem: histological signs of AFLP	38.2	Maternal mortality: 0.13/100,000 live births Maternal morbidity: 3.2/100,000 deliveries Perinatal mortality rate: 22.7% Incidence: 3.2/100,000 births

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Reference	Nature of the study	Objectives	number of inclusion	number of AFLP	Diagnosis of AFPL	WG at diagnosis mean +/- SD (wk)	Main results
	2-year retrospective and multicenter	To assess severe maternal morbidity	371,021 deliveries	12	Clinical and biological diagnosis	34.5	
Lau <i>et al.</i> [24]	22-year retrospective and single-center	To evaluate the demographics, clinical presentations, laboratory findings, and maternal and fetal outcomes	136,214 deliveries	18	acute hepatic failure in the 3 rd trimester, abdominal pain, nausea or vomiting, laboratory evidence of hepatic failure, signs of coagulopathy	35.6 ±2.8	Risk factors for complications: Morbidities: acute renal failure, hypoglycemia, DIC Maternal death: 11% Perinatal mortality rate: 18% Incidence: 1/7,568 births
Goel <i>et al.</i> [33]	8-year retrospective and single-center	To assess the accuracy of the Swansea criteria to predict hepatic microvesicular steatosis in patients with suspected pregnancy-related liver disease	34	24	Swansea criteria versus histological examination	36	20 patients fulfilled Swansea criteria for AFLP Sensitivity of Swansea criteria for microvesicular steatosis: 100% Specificity and Sensitivity of Swansea criteria for microvesicular steatosis: 57%

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Reference	Nature of the study	Objectives	number of inclusion	number of AFLP	Diagnosis of AFPL	WG at diagnosis mean +/- SD (wk)	Main results
Knight <i>et al.</i> [17]	20-month retrospective from 229 UK hospitals	To evaluate proposed diagnostic criteria, to accurately document the incidence, management, and outcomes	80	57	Symptoms and signs consistent with AFLP or AFLP confirmed by biopsy or postmortem	Median 36	Risk factors for complications: Twin pregnancies and low BMI Maternal death: 1.8% Perinatal mortality rate: 10.4% Incidence of 1/20,000 births

REFERENCES

- [1] García-Romero CS, Guzman C, Cervantes A, Cerbón M. Liver disease in pregnancy: Medical aspects and their implications for mother and child. *Ann Hepatol* 2019;18:553–62. <https://doi.org/10.1016/j.aohep.2019.04.009>.
- [2] Sheehan HL. The Pathology of Acute Yellow Atrophy and Delayed Chloroform Poisoning. *BJOG Int J Obstet Gynaecol* 1940;47:49–62. <https://doi.org/10.1111/j.1471-0528.1940.tb14731.x>.
- [3] Knox TA, Olans LB. Liver disease in pregnancy. *N Engl J Med* 1996;335:569–76. <https://doi.org/10.1056/NEJM199608223350807>.
- [4] Ibdah J-A. Acute fatty liver of pregnancy: an update on pathogenesis and clinical implications. *World J Gastroenterol* 2006;12:7397–404.
- [5] Ahmed KT, Almashhrawi AA, Rahman RN, Hammoud GM, Ibdah JA. Liver diseases in pregnancy: diseases unique to pregnancy. *World J Gastroenterol* 2013;19:7639–46. <https://doi.org/10.3748/wjg.v19.i43.7639>.
- [6] Nelson DB, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: clinical outcomes and expected duration of recovery. *Am J Obstet Gynecol* 2013;209:456.e1-7. <https://doi.org/10.1016/j.ajog.2013.07.006>.
- [7] Ch'ng CL, Morgan M, Hainsworth I, Kingham JGC. Prospective study of liver dysfunction in pregnancy in Southwest Wales. *Gut* 2002;51:876–80.
- [8] Goel A, Jamwal KD, Ramachandran A, Balasubramanian KA, Eapen CE. Pregnancy-related liver disorders. *J Clin Exp Hepatol* 2014;4:151–62. <https://doi.org/10.1016/j.jceh.2013.03.220>.
- [9] Liu J, Ghaziani TT, Wolf JL. Acute Fatty Liver Disease of Pregnancy: Updates in Pathogenesis, Diagnosis, and Management. *Am J Gastroenterol* 2017;112:838–46. <https://doi.org/10.1038/ajg.2017.54>.
- [10] Wei Q, Zhang L, Liu X. Clinical diagnosis and treatment of acute fatty liver of pregnancy: a literature review and 11 new cases. *J Obstet Gynaecol Res* 2010;36:751–6. <https://doi.org/10.1111/j.1447-0756.2010.01242.x>.
- [11] Vigil-de Gracia P, Montufar-Rueda C. Acute fatty liver of pregnancy: diagnosis, treatment, and outcome based on 35 consecutive cases. *J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet* 2011;24:1143–6. <https://doi.org/10.3109/14767058.2010.531325>.
- [12] Fromenty B, Pessayre D. Inhibition of mitochondrial beta-oxidation as a mechanism of hepatotoxicity. *Pharmacol Ther* 1995;67:101–54.
- [13] Ibdah JA, Bennett MJ, Rinaldo P, Zhao Y, Gibson B, Sims HF, et al. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. *N Engl J Med* 1999;340:1723–31. <https://doi.org/10.1056/NEJM199906033402204>.
- [14] Yang Z, Yamada J, Zhao Y, Strauss AW, Ibdah JA. Prospective screening for pediatric mitochondrial trifunctional protein defects in pregnancies complicated by liver disease. *JAMA* 2002;288:2163–6.
- [15] Browning MF, Levy HL, Wilkins-Haug LE, Larson C, Shih VE. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. *Obstet Gynecol* 2006;107:115–20. <https://doi.org/10.1097/01.AOG.0000191297.47183.bd>.
- [16] Natarajan SK, Ibdah JA. Role of 3-Hydroxy Fatty Acid-Induced Hepatic Lipotoxicity in Acute Fatty Liver of Pregnancy. *Int J Mol Sci* 2018;19. <https://doi.org/10.3390/ijms19010322>.

- 1 [17] Knight M, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P, UK Obstetric
2 Surveillance System. A prospective national study of acute fatty liver of pregnancy in
3 the UK. *Gut* 2008;57:951–6. <https://doi.org/10.1136/gut.2008.148676>.
- 4 [18] Vigil-De Gracia P. Acute fatty liver and HELLP syndrome: two distinct pregnancy
5 disorders. *Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet* 2001;73:215–20.
- 6 [19] Reyes H, Sandoval L, Wainstein A, Ribalta J, Donoso S, Smok G, et al. Acute fatty liver
7 of pregnancy: a clinical study of 12 episodes in 11 patients. *Gut* 1994;35:101.
- 8 [20] Kingham JGC. Swansea criteria for diagnosis of acute fatty liver of pregnancy. *Gut*
9 2010. <https://doi.org/10.1136/gut.2010.222240>.
- 10 [21] Morton A. Presumed acute fatty liver of pregnancy following influenza A hepatitis.
11 *Obstet Med* 2017;10:186–8. <https://doi.org/10.1177/1753495X17695173>.
- 12 [22] Zhang Y-P, Kong W-Q, Zhou S-P, Gong Y-H, Zhou R. Acute Fatty Liver of Pregnancy:
13 A Retrospective Analysis of 56 Cases. *Chin Med J (Engl)* 2016;129:1208–14.
14 <https://doi.org/10.4103/0366-6999.181963>.
- 15 [23] Mellouli MM, Amara FB, Maghrebi H, Bouchnack M, Khaled N, Rezigia H. Acute fatty
16 liver of pregnancy over a 10-year period at a Tunisian tertiary care center. *Int J Gynaecol
17 Obstet Off Organ Int Fed Gynaecol Obstet* 2012;117:88–9.
18 <https://doi.org/10.1016/j.ijgo.2011.11.012>.
- 19 [24] Lau H-H, Chen Y-Y, Huang J-P, Chen C-Y, Su T-H, Chen C-P. Acute fatty liver of
20 pregnancy in a Taiwanese tertiary care center: a retrospective review. *Taiwan J Obstet
21 Gynecol* 2010;49:156–9. [https://doi.org/10.1016/S1028-4559\(10\)60033-2](https://doi.org/10.1016/S1028-4559(10)60033-2).
- 22 [25] Bernuau J, Degott C, Nouel O, Rueff B, Benhamou JP. Non-fatal acute fatty liver of
23 pregnancy. *Gut* 1983;24:340–4.
- 24 [26] Sibai BM. Imitators of severe preeclampsia. *Obstet Gynecol* 2007;109:956–66.
25 <https://doi.org/10.1097/01.AOG.0000258281.22296.de>.
- 26 [27] Hay JE. Liver disease in pregnancy. *Hepatol Baltim Md* 2008;47:1067–76.
27 <https://doi.org/10.1002/hep.22130>.
- 28 [28] Meng J, Wang S, Gu Y, Lv H, Jiang J, Wang X. Prenatal predictors in postpartum
29 recovery for acute fatty liver of pregnancy: experiences at a tertiary referral center. *Arch
30 Gynecol Obstet* 2016;293:1185–91. <https://doi.org/10.1007/s00404-015-3941-5>.
- 31 [29] Gao H-Z, Kobayashi K, Tabata A, Tsuge H, Iijima M, Yasuda T, et al. Identification of
32 16 novel mutations in the argininosuccinate synthetase gene and genotype-phenotype
33 correlation in 38 classical citrullinemia patients. *Hum Mutat* 2003;22:24–34.
34 <https://doi.org/10.1002/humu.10230>.
- 35 [30] Gao Q, Qu X, Chen X, Zhang J, Liu F, Tian S, et al. Outcomes and risk factors of
36 patients with acute fatty liver of pregnancy: a multicentre retrospective study. *Singapore
37 Med J* 2018;59:425–30. <https://doi.org/10.11622/smedj.2018001>.
- 38 [31] Maitra A, Domiati-Saad R, Yost N, Cunningham G, Rogers BB, Bennett MJ. Absence
39 of the G1528C (E474Q) mutation in the alpha-subunit of the mitochondrial trifunctional
40 protein in women with acute fatty liver of pregnancy. *Pediatr Res* 2002;51:658–61.
41 <https://doi.org/10.1203/00006450-200205000-00019>.
- 42 [32] Zhou G, Zhang X, Ge S. Retrospective analysis of acute fatty liver of pregnancy:
43 twenty-eight cases and discussion of anesthesia. *Gynecol Obstet Invest* 2013;76:83–9.
44 <https://doi.org/10.1159/000351565>.
- 45 [33] Goel A, Ramakrishna B, Zachariah U, Ramachandran J, Eapen CE, Kurian G, et al. How
46 accurate are the Swansea criteria to diagnose acute fatty liver of pregnancy in predicting
47 hepatic microvesicular steatosis? *Gut* 2011;60:138–9; author reply 139-140.
48 <https://doi.org/10.1136/gut.2009.198465>.
- 49 [34] Treem WR. Mitochondrial fatty acid oxidation and acute fatty liver of pregnancy. *Semin
50 Gastrointest Dis* 2002;13:55–66.

- 1 [35] Cheng N, Xiang T, Wu X, Li M, Xie Y, Zhang L. Acute fatty liver of pregnancy: a
2 retrospective study of 32 cases in South China. *J Matern-Fetal Neonatal Med Off J Eur*
3 *Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet* 2014;27:1693–7.
4 <https://doi.org/10.3109/14767058.2013.871704>.
- 5 [36] Bacq Y. Liver diseases unique to pregnancy: a 2010 update. *Clin Res Hepatol*
6 *Gastroenterol* 2011;35:182–93. <https://doi.org/10.1016/j.clinre.2010.11.011>.
- 7 [37] Mansouri A, Fromenty B, Durand F, Degott C, Bernuau J, Pessayre D. Assessment of
8 the prevalence of genetic metabolic defects in acute fatty liver of pregnancy. *J Hepatol*
9 1996;25:781.
- 10 [38] Grimbert S, Fisch C, Deschamps D, Berson A, Fromenty B, Feldmann G, et al. Effects
11 of female sex hormones on mitochondria: possible role in acute fatty liver of pregnancy.
12 *Am J Physiol* 1995;268:G107-115. <https://doi.org/10.1152/ajpgi.1995.268.1.G107>.
- 13 [39] Lamprecht A, Morton A, Laurie J, Lee W. Acute fatty liver of pregnancy and
14 concomitant medical conditions: A review of cases at a quaternary obstetric hospital.
15 *Obstet Med* 2018;11:178–81. <https://doi.org/10.1177/1753495X18764816>.
- 16 [40] Anon B, Barbet C, Gendrot C, Labarthe F, Bacq Y. [Acute fatty liver of pregnancy and
17 mitochondrial fatty acid oxidation. Consequences for the offspring]. *Arch Pediatr*
18 *Organe Off Soc Francaise Pediatr* 2017. <https://doi.org/10.1016/j.arcped.2017.05.012>.
- 19 [41] Kong X-F, Zhang X-X, Yu Y-Y, Shi Q, La D-D, Zhu-Ge C-D, et al. No mutation was
20 found in the alpha-subunit of the mitochondrial tri-functional protein in one patient with
21 severe acute fatty liver of pregnancy and her relatives. *J Gastroenterol Hepatol*
22 2007;22:2107–11. <https://doi.org/10.1111/j.1440-1746.2006.04682.x>.
- 23 [42] Lin L, Chen Y-H, Sun W, Gong J-J, Li P, Chen J-J, et al. Risk factors of obstetric
24 admissions to the intensive care unit: An 8-year retrospective study. *Medicine*
25 *(Baltimore)* 2019;98:e14835. <https://doi.org/10.1097/MD.00000000000014835>.
- 26 [43] Allen AM, Kim WR, Larson JJ, Rosedahl JK, Yawn BP, McKeon K, et al. The
27 Epidemiology of Liver Diseases Unique to Pregnancy in a US Community: A
28 Population-Based Study. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol*
29 *Assoc* 2016;14:287-294.e1-2. <https://doi.org/10.1016/j.cgh.2015.08.022>.
- 30 [44] Dekker RR, Schutte JM, Stekelenburg J, Zwart JJ, van Roosmalen J. Maternal mortality
31 and severe maternal morbidity from acute fatty liver of pregnancy in the Netherlands.
32 *Eur J Obstet Gynecol Reprod Biol* 2011;157:27–31.
33 <https://doi.org/10.1016/j.ejogrb.2011.02.015>.
- 34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

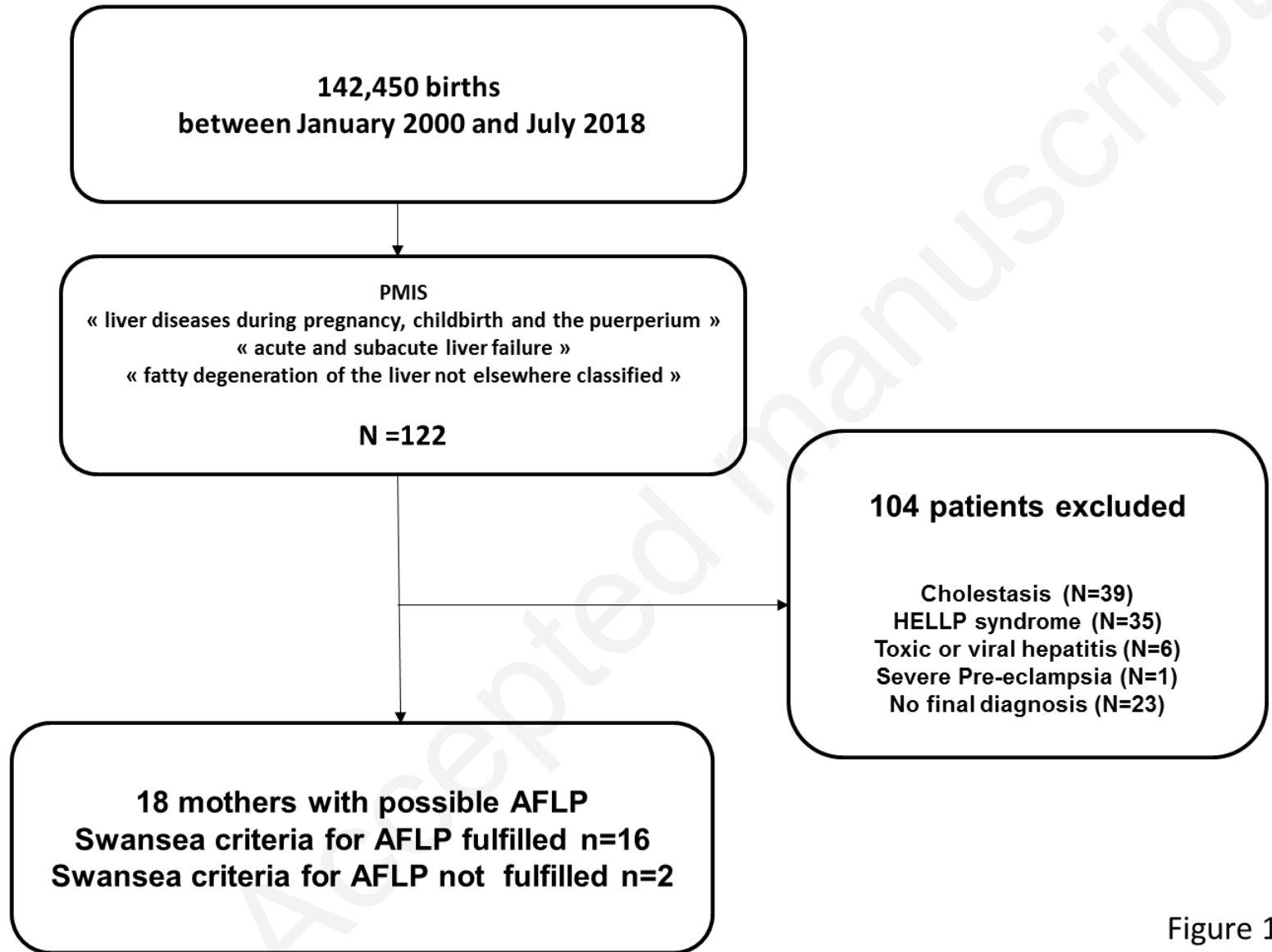
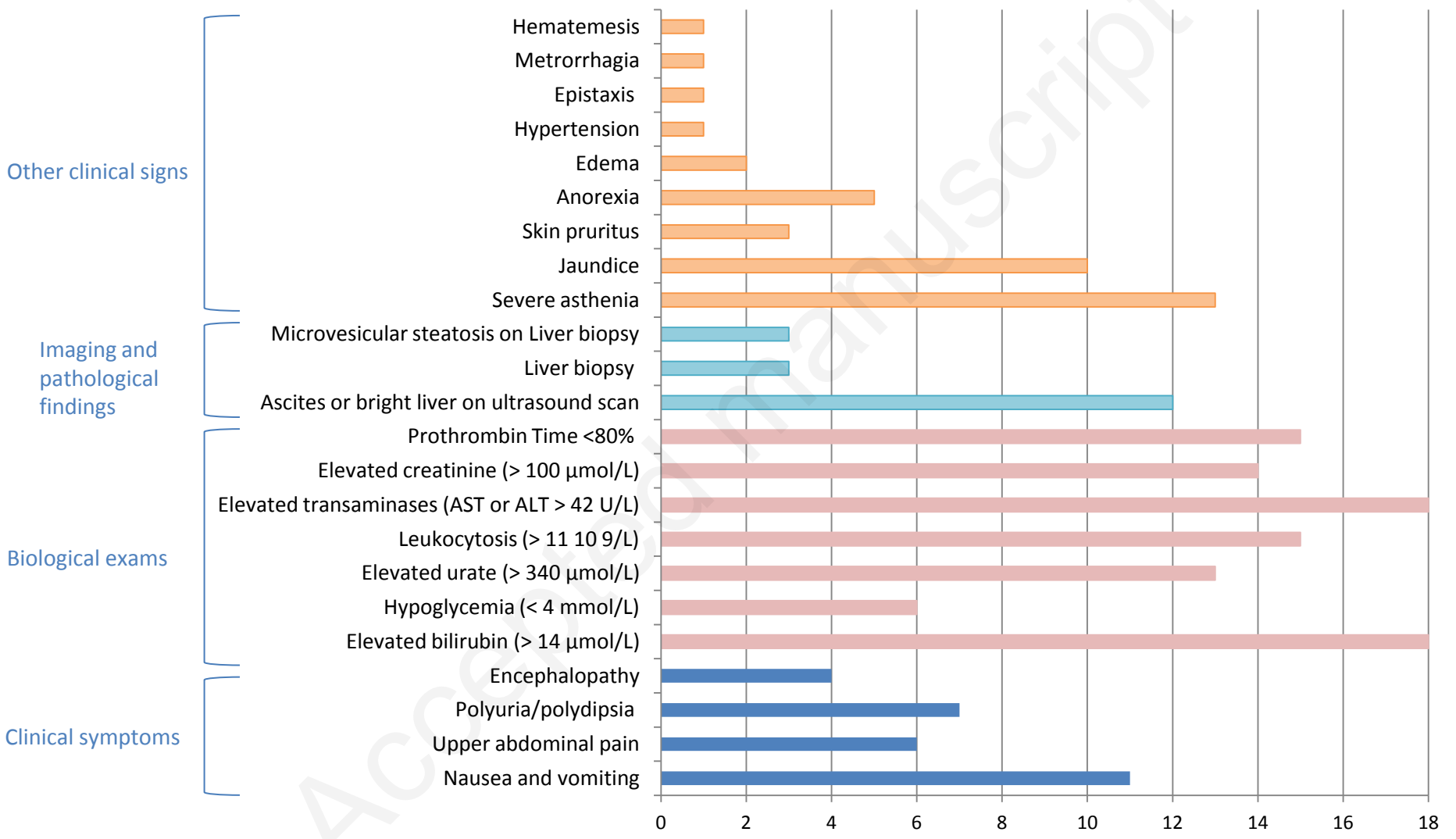


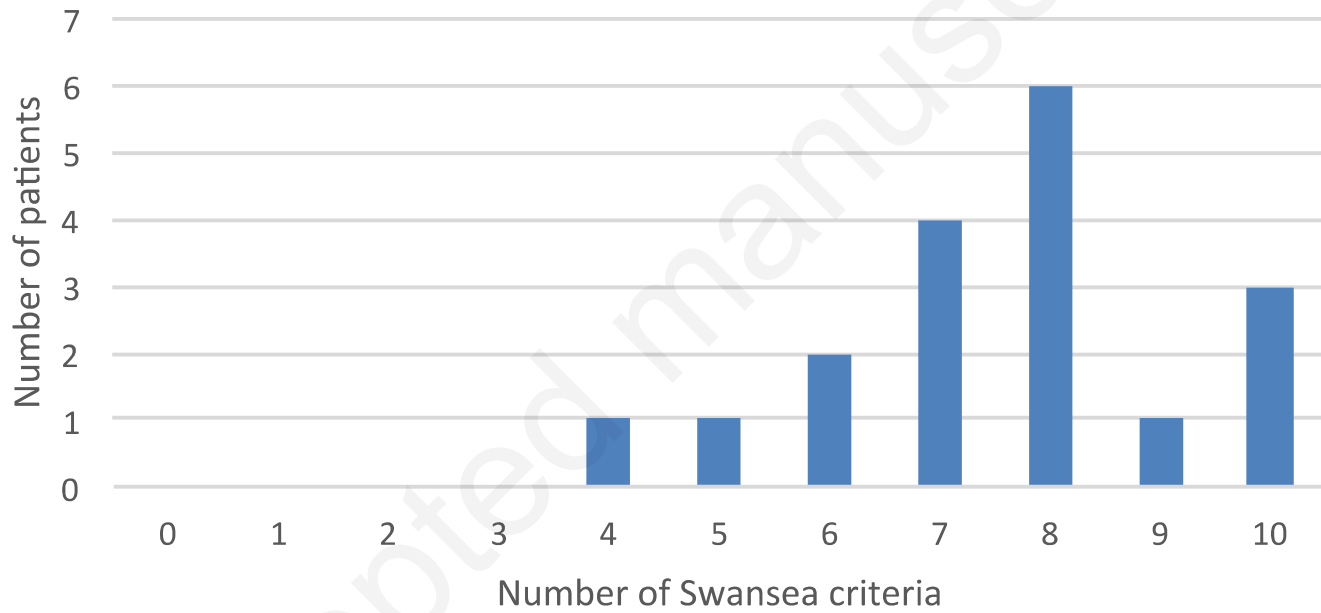
Figure 1

Figure
FIGURE 2A



AST = aspartate aminotransferase, ALT = alanine aminotransferase

FIGURE 2B



DISCLOSURE OF ANY SOURCE OF FINANCIAL SUPPORT OF THE STUDY: The authors have no disclosures to declare. We did not get any funding for this project. They have no conflict of interest to declare.

Accepted manuscript

1 **Maternal and neonatal outcomes and prognostic factors in acute fatty liver**
2 **of pregnancy**

3
4 Y Joueidi ^{1*}, K Peoc'h ^{2,3*}, M Le Lous ¹, G Bouzille ⁴, C Rousseau ⁵, E Bardou-Jacquet ^{6,7}, C
5 Bendavid ^{7,8}, L Damaj⁹, B Fromenty ⁷, V Lavoué ^{1,10}, C Moreau ^{8,10}

6
7 ¹ Service de Gynécologie obstétrique, Hôpital Sud CHU Rennes, France

8 ² APHP, HUPNVS, UF de Biochimie Clinique, Hôpital Beaujon, F-91118, Clichy, France

9 ³ Université de Paris, UFR de Médecine Xavier Bichat Centre de Recherche sur
10 l'Inflammation (CRI), F-75018 Paris, France.

11 ⁴ PMSI, Hôpital Pontchaillou CHU Rennes, 2 rue Henri Le Guilloux, 35000 Rennes, France.

12 ⁵ Service de recherche clinique, Hôpital Pontchaillou CHU Rennes, 2 rue Henri Le Guilloux,
13 35000 Rennes, France.

14 ⁶ Service d'Hépatologie, Hôpital Pontchaillou CHU Rennes, 2 rue Henri Le Guilloux, 35000
15 Rennes, France.

16 ⁷ Univ Rennes, INSERM, INRA, Institut NuMeCan, CHU Rennes, France

17 ⁸ Laboratoire de Biochimie-Toxicologie, Hôpital Pontchaillou CHU Rennes, 2 rue Henri Le
18 Guilloux, 35000 Rennes, France.

19 ⁹ Service de Pédiatrie, Hôpital Sud, CHU Rennes Boulevard de Bulgarie, 35000 Rennes,
20 France

21 ¹⁰ Univ Rennes, CHU Rennes, INSERM, EHESP, IRSET (Institut de Recherche en Santé,
22 Environnement et Travail) UMR_S 1085, F-35000 Rennes, France

23
24 *The two first authors collaborated equally to work.

25
26
27
28 **Corresponding author**
29 Dr. Caroline Moreau
30 Laboratoire de Biochimie-Toxicologie
31 Hôpital Pontchaillou – CHU Rennes
32 2, rue Henri Le Guilloux
33 35033 Rennes Cedex
34 Tel: 0033299284275
35 Mail: caroline.moreau@chu-rennes.fr

36
37
38
39 6030 words
40

1 **ABSTRACT**

2 Objective: To report complications of Acute Fatty Liver of pregnancy (AFLP), rare liver
3 disease of pregnancy, and identify prognostic factors for mothers and children.

4 Study Design: We conducted a retrospective descriptive study between January 2000 and July
5 2018 in three French maternity centers. Demographic, clinical, biological data, and outcomes
6 of patients and their infants were reviewed.

7 Results: 142,450 pregnancies from three French maternity centers were studied. Eighteen
8 patients with AFLP were identified for over 18 years. The incidence of AFLP was estimated
9 as 1/7,914 pregnancies. Prolonged prothrombin time, expressed as ratio was identified as a
10 risk factor of maternal complications (OR=0.86, 95% CI (0.73-1.00), $p = 0.0493$). Gestational
11 age at delivery was the only risk factor associated with fetal or neonate complications
12 (OR=0.37, 95% CI (0.14-0.96), $p = 0.0417$). One boy died of previously diagnosed β -
13 oxidation deficiency at eight months.

14 Conclusion: In AFLP, the finding of a prolonged prothrombin time may suggest an increased
15 risk for major maternal complications and must be carefully monitored. Infants born to
16 mothers with ALFP should be screened as early as possible for mitochondrial fatty acid
17 oxidation deficiency.

18

19

20 **Keywords:** acute fatty liver of pregnancy, Swansea criteria, metabolic disease, liver, delivery,
21 fetal and maternal outcomes

22

23

24

1 INTRODUCTION

2 The prevalence of liver diseases in pregnancy is estimated at near 3% of all pregnancies in
3 developed countries[1], including liver diseases induced by pregnancy or those revealed
4 during pregnancy. Five liver disorders are specific to pregnancy: *hyperemesis gravidarum*,
5 intrahepatic cholestasis, liver disorders associated with pre-eclampsia (PE), Hemolysis,
6 Elevated Liver enzymes, and Low Platelet count syndrome (HELLP), and Acute Fatty Liver
7 of pregnancy (AFLP). AFLP, initially described in 1940 [2], typically occurs during the third
8 trimester of pregnancy, with an incidence ranging between 1/5,000 and 1/20,000 pregnancies
9 [3–6]. This disease combines non-specific symptoms as nausea, vomiting or headache, and
10 laboratory findings, including elevated transaminases, coagulopathy, and renal impairment.
11 Because of these non-specific characteristics, there is a lack of international consensus for the
12 diagnosis of AFLP. In the literature, diagnostic criteria for AFLP known as the Swansea
13 criteria have been proposed by Ch'ng *et al.* as a means to distinguish AFLP from other causes
14 of liver dysfunction, including HELLP, but these have not been extensively validated and
15 remain still debated [7–9].

16 Moreover, the pathophysiology of AFLP remains unclear. The origin seems to be
17 multifactorial but mitochondrial dysfunction might be the essential cause. Different
18 investigations point to severe mitochondrial dysfunction in the liver in the case of AFLP [10].
19 The authors suggested that oxidation of fatty acids decreased at the end of gestation, because
20 of morphological abnormalities of hepatic mitochondria. This modification of liver cell
21 function might be due to sex hormones such as estradiol and progesterone that inhibited the
22 mitochondrial beta-oxidation [10]. One other hypothesis is that high cytokines in an infectious
23 context can impair mitochondrial function [11]. Finally, the association of fetal fatty acid
24 oxidation defects with maternal liver disease [8], could be triggered by several genetic and
25 acquired factors [9]. Long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) deficiency

1 might play a role in some cases of AFLP [4,12–15]. Some authors suggested that the
2 accumulated 3-hydroxy-fatty acids in the mother's liver might be causative, perhaps as a
3 maternal hepatic toxin [16].

4 To our knowledge, little data exist regarding the description of maternal and fetal outcomes of
5 AFLP. In 2018, Gao *et al.* aimed to describe the characteristics of AFLP and assessed the
6 outcomes and risk factors of the mother and fetus [17]. They concluded that the history of
7 legal termination of pregnancy was the higher risk factor for maternal mortality. More
8 recently, Chang *et al.* conducted a retrospective study to describe the frequency of negative
9 maternal and fetal outcomes [18]. They found that patients with worse outcomes were
10 younger, had a singleton, the increased value of ALT and bilirubin, and prolonged
11 prothrombin time. We conducted a multicenter retrospective study over 18 years to report
12 maternal and perinatal outcomes of AFLP, and identify prognostic factors for mothers and
13 children.

15 **METHODS**

16 Design

17 We performed a multicenter retrospective study between January 1st, 2000, and July 31st,
18 2018, in three maternity centers of the west of France: Rennes, Vannes, and Saint-Brieuc. We
19 performed data mining on the program of the medicalization of information systems (PMIS),
20 using the following research criteria "liver diseases during pregnancy, childbirth, and
21 puerperium," "acute and subacute liver failure" and "fatty degeneration of the liver not
22 elsewhere classified." Approval for the study was obtained from a local institutional review
23 board.

24 Patients

1 For the analysis of features and outcomes, we included all patients with a diagnosis of AFLP
2 based on the diagnosis of the treating clinician and/or declared in the PMIS. The diagnosis of
3 AFLP was based on the association of clinical and biological data. AFLP was diagnosed if
4 patients had nausea, vomiting or headache, elevated transaminases, coagulopathy, and renal
5 impairment. AFLP was defined as a certain diagnosis after the exclusion of any other liver
6 disease of pregnancy as intrahepatic cholestasis of pregnancy, toxic or viral hepatitis, HELLP
7 syndrome, PE, or preexisting liver disease. The diagnosis of AFLP was retained if an
8 alternative diagnosis could not be made. All patients with diagnosed AFLP were included
9 regardless of gestational age or kind of pregnancy (singleton or multiple pregnancies). *A*
10 *posteriori*, and for each patient with a diagnosis of AFLP, a study investigator (YJ) reviewed
11 the clinical, biological, imaging, and pathological data to include or exclude patients.

12 Data collection

13 Maternal data included: age at diagnosis, parity, gravidity, consanguinity, ethnicity, medical
14 antecedents (hypertension, diabetes, hypercholesterolemia, preexisting liver disease),
15 obstetrical history (cholestasis, AFLP, PE, HELLP, cicatricial uterus), body mass index
16 (BMI) and mode of delivery. Maternal laboratory data collected at admission included:
17 aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, blood urea
18 nitrogen (BUN), estimated glomerular filtration rate (eGFR), serum and urine total proteins,
19 alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), whole and conjugated
20 bilirubin, bile acid, lactate dehydrogenase (LDH), uric acid, haptoglobin, glycemia,
21 hemoglobin, platelets, leukocytes, prothrombin time ratio (PT), fibrinogen, factor 5 (or
22 proaccelerin that reflects both coagulation disorders and liver function disorders), and
23 hepatitis serology. Medical imaging data included ultrasounds and computerized tomography.
24 Pathological data concerned liver biopsy results and placenta examination. Data collected for
25 the infants included birth weight, Apgar score, sex, pH and lactate at birth, and molecular

1 diagnosis of LCHAD deficiency. We recorded maternal and fetal complications and their
2 outcomes.

3 Outcome measures

4 Our primary outcome for mothers was a serious maternal complication: Intensive Care Unit
5 hospitalization (ICU), long stay in ICU (more than 2 days of hospitalization), disseminated
6 intravascular coagulation (DIC), pleural effusion, ascites, hemorrhage, and/or acute kidney
7 injury.

8 The primary outcome for the fetuses or neonates was intrauterine death (IUD) and admission
9 to the neonatal intensive care unit (NICU) immediately after birth.

10 Statistical analysis

11 A descriptive statistical analysis was performed on SAS software (v 9.4). All demographic,
12 clinical and biological data were analyzed in statistical analysis. Qualitative data were
13 expressed in number (n) and percentage (%); the quantitative variables were described as
14 follows: N, the minimum and maximum values, medians, and interquartile (IQ) ranges. All
15 variables with a p-value < 0.10 are presented in Table 3. We considered variables with a p-
16 value lower than 0.05 as significant in univariate analysis.

17 Univariate logistic regressions were performed on each variable to examine the association
18 between clinical, biological, imaging, and pathology data with adverse maternal and neonatal
19 outcomes. For this latter analysis, twin-pregnancies were excluded.

20 For logistic regression, the severity criteria in the mothers included in the model were: DIC,
21 pleural effusion/ascites, hemorrhage, and malignant hypertension, and severity criteria for the
22 fetuses or neonates included were IUD and NICU admission.

23

24

25 **RESULTS**

1 Description of the population

2 A total of 142,450 pregnancies were recorded in the regional center's neonatal screening
3 registry (covering the three French maternity centers cited above) between January 1st, 2000
4 and July 31st, 2018. After exclusion, we identified 122 records of pregnancies using the
5 criteria mentioned previously for AFLP inclusion. One hundred and four women were
6 excluded as they suffered from other preexisting liver diseases or liver disease of pregnancy
7 that was not AFLP, or because of a lack of final diagnosis (**Figure 1**). Eighteen patients were
8 finally diagnosed as suffering from AFLP, giving an estimated incidence of 1 case per 7,914
9 pregnancies. The mother's baseline characteristics are reported in **Table 1**. Eleven patients
10 (61%) were primiparous. It was the first pregnancy for nine of them (50%). The median age at
11 diagnosis was 27.5 (IQ 26-29.8). One mother had a clinical history of intrahepatic cholestasis
12 of pregnancy (5.6%) for a previous pregnancy. None of the patients had major medical or
13 surgical events before the pregnancy. The median BMI was 21.5 kg/m² (IQ: 20.3-24.9; n=15),
14 and three patients presented a BMI < 19 kg/m² (20%). One of the pregnancies was a
15 spontaneous bichorial twin pregnancy (5.6%). The median gestational age at diagnosis was
16 35.2 weeks of gestation (WG) (IQ 33.1-37.9). Ten neonates were male (52.6%).

17 Initial presentation and Swansea criteria in mothers

18 Clinical, biological characteristics and Swansea criteria are summarized in **Table 1 and**
19 **Figure 2A**. The repartition of Swansea criteria in the study population is presented in **Figure**
20 **2B**. Sixteen patients (89%) experienced prodromal syndrome: nausea and vomiting (61%),
21 abdominal pain (33%), polyuria-polydipsia syndrome (39%), and encephalopathy (22%).
22 Other symptoms at diagnosis included severe asthenia (72%) defined as significant exhaustion
23 in the absence of any effort, not improved by rest, jaundice (56%), anorexia (28%), episodes
24 of confusion (22%), and skin pruritus (17%).

25

1 The biological results are detailed in **Table 1**. Hypoglycemia was reported for six patients
2 (33%). All patients presented hepatic cytolysis with **ALT > AST** in 11 patients out of 18
3 (61%). All patients had bilirubin higher than 14 $\mu\text{mol/L}$. Low concentrations of fibrinogen
4 were observed in 82 % (reference values: 3.7 to 6.2 g/L in the third trimester of pregnancy). A
5 prolonged prothrombin time (PT; **expressed as ratio**) was observed in 15 patients (83%)
6 (Range: 18-96%). Fourteen patients (78%) exhibited an acute kidney injury with a creatinine
7 higher than 100 $\mu\text{mol/L}$, and 50% of patients > 150 $\mu\text{mol/L}$.
8 The leukocytes counts were higher than 11 G/L in 15 of the patients (83%). Overall, 100% of
9 the patients presented elevated transaminase and bilirubin levels.
10 Liver ultrasound was performed in fourteen of the 18 patients (78%). Nine out of the 14
11 patients with hepatic imaging data (64%) presented a hyperechoic liver compatible with
12 hepatic steatosis without dilatation of bile ducts. Three patients (20%) had ascites.
13 A liver biopsy was performed in three patients (17%) demonstrating, in each case, the
14 presence of microvesicular steatosis.
15 The number of Swansea criteria ranged between 4 and 10. Sixteen patients (89%) presented
16 six or more Swansea criteria (**Figure 2B**).

17 Deliveries

18 The vaginal delivery rate was 11% (two patients in labor at admission **with prompt**
19 **deliveries**). All births occurred within 48 hours after the admission. **Three patients received**
20 **steroids in the prevention of prematurity-related complications**. In one patient, the diagnosis
21 of AFLP was not evident on the day of hospitalization and was made after clinical and
22 biological monitoring.

23 Maternal Outcomes

24 The maternal outcomes are summarized in **Table 2**. Fourteen mothers (78%) were
25 hospitalized in the ICU for an average length of stay of 2.2 ± 2.2 days (1 to 8 days). Severe

1 complications were: DIC (33%), pleural effusion/ascites (17%), acute kidney failure (78%) or
2 hemorrhage (17%), including retroperitoneal hematoma, cataclysmic hemorrhage, and
3 hemoperitoneum requiring surgical revision. No maternal death was reported, and no mothers
4 needed dialysis or liver transplantation. Coagulation disorders were not systematically
5 associated with the severity of the hepatic cytolysis (correlation between PT and ALT, $r=-$
6 0.169 $p=0.4891$; correlation between PT and AST $r=-0.4294$ $p=0.0666$). Among the seven
7 cases of severe maternal complications, there were five cases of severe fetal complications;
8 among the 10 cases with no severe maternal complications, there were five cases of severe
9 fetal complications.

10 Univariate analysis identified that an increased PT was associated with lower severe maternal
11 complications (OR = 0.86 [CI 95% 0.73; 1.00] $p=0.0493$) (**Table 3**); *i.e.*, a decreased PT is
12 linked with severe maternal complication. Of note, concerning the association between parity
13 and maternal complications, the reference relates to women with previous deliveries
14 compared with nulliparous women.

15 Fetal and infant outcomes

16 The neonatal outcomes are summarized in **Table 2**. Thirteen children (68.4%) were born
17 prematurely, five of them (38.5%) before 34 WG, and eight (61.5%) between 34 and 37 WG.
18 The median birth weight of the neonates was 2,415 g (IQ: 2,015-2,790). Birth weight of less
19 than 2,000 g was observed in 21% of neonates. One suffered from fetal growth restriction
20 ($<10^{\text{th}}$ percentile). Ten children (52.6%) were hospitalized in the NICU. Two fetuses died *in*
21 *utero*. In both cases, an emergency cesarean section was performed because of maternal
22 multiorgan failure. None of the neonates died during the initial hospitalization, and one infant
23 died at eight months.

24 Lower severe complications in the neonates were associated with advanced gestational age at
25 delivery (OR = 0.37 [CI 95% 0.14; 0.96] $p=0.0417$) (**Table 3**), *i.e.*, severe complications in

1 the neonates were associated with an early gestational age at delivery. The frequency of
2 complications decreased as the gestational age at birth increased.

3 Outcome after the acute episode

4 Maternal biological data normalized within the month following delivery without any organic
5 sequelae for mothers.

6 All neonates displayed initial healthy development. At eight months, one infant presented
7 with episodes of ocular revulsion, limb hypertonicity, and axial hypotonia secondary to
8 prolonged fasting as part of an infection. The child died of cardiorespiratory arrest with
9 hepatic encephalopathy and hypertrophic cardiomyopathy. LCHAD deficiency caused by a
10 mutation in the *HADHA* gene was identified in this child. The only other child screened for
11 *HADHA* mutation did not exhibit any variant.

12

1 DISCUSSION

2 AFLP is a rare but life-threatening complication occurring typically during the third trimester
3 of pregnancy. In our cohort, eighteen mothers with AFLP were identified over an 18 years
4 period, giving an estimated incidence of one case for 7,914 pregnancies, similar to that of
5 previous studies [19] (**Supplementary Table 1**).

6 Some authors highlight risk factors for developing AFLP. Primiparity [20], multiple
7 pregnancies [21–23], male sex of the fetus [19,24,25], history of AFLP [26], and the existence
8 of another related liver disease during pregnancy [27] are thus described as risk factors for
9 AFLP.

10 Diagnosis of AFLP is commonly based on the Swansea criteria, or on the AFLP-Triad
11 described by Vigil-De Gracia [28]. In our population, 16 patients presented with six to ten
12 Swansea criteria. For the two mothers with less than six criteria, HELLP syndrome or other
13 liver diseases were rejected. Indeed, in previous cohorts, a small percentage of *bona fide* cases
14 of AFLP did not fulfill the Swansea criteria [19,29]. Fifteen mothers exhibited prolonged PT;
15 all exhibited elevated transaminases (>46 IU/L), and bilirubin (>14 µmol/L) that should be
16 considered as arguments for the diagnosis. Hyperechogenicity of the liver on liver ultrasound
17 scans that we observed in 64% of the patients is an additional argument for diagnosis
18 [20,30,31].

19 Timely fetal extraction is mandatory to improve both maternal and fetal prognosis [27,32].
20 There is no consensus for the way of delivery. Still, the cesarean section seems to be
21 associated with a lower risk of peripartum mortality in this context and should be the
22 preferred method to terminate the pregnancy if vaginal delivery can not be made promptly
23 [27].

24 In our cohort, two fetuses (10.5%) died *in utero*, which is in the range of previously described
25 fetal mortality [13,14,33]. Gestational age at delivery was identified as the only risk factor

1 associated with fetal or neonatal complications (OR=0.37, 95% CI (0.14-0.96), $p = 0.0417$).

2 Early gestational age at diagnosis was correlated with more neonatal complications. This

3 factor was previously identified in a Chinese cohort as a factor of perinatal death [20]. It

4 remains to be established whether this observation is relative to AFLP or secondary to

5 complications of prematurity.

6 To date, maternal mortality in AFLP is estimated at around 2% [7,27,34]. We observed no

7 maternal death in our cohort. We identify that prolonged PT was significantly associated with

8 a risk of severe maternal complications (OR = 0.86, 95% CI (0.73-1.00), $p = 0.0493$). This

9 defect in the coagulation pathway is likely due to the hepatocellular deficiency related to the

10 primary injury of the liver, and possibly to the accumulation of some long-chain hydroxy-

11 fatty acids [15]. A lack of coagulation proteins has been previously identified as a risk factor

12 for severe complications in AFLP [20,23,35]. Zhang *et al.* and Gao *et al.* also observed an

13 association between PT and maternal complications in AFLP [17,20]. In a recent publication,

14 Chang *et al.* found that younger mother, singleton pregnancy, higher ALT and bilirubin

15 concentration, lower PT activity were risk factors for negative fetal outcomes [18].

16 In our population, an 8-month old boy died of LCHAD deficiency. LCHAD deficiency

17 (OMIM 609016) has previously been reported in children born from mothers suffering from

18 AFLP [4,13,15,36]. However, the incidence of LCHAD deficiency is 1/100,000, which is

19 lower than AFLP. The etiology of AFLP is probably multifactorial, involving maternal and

20 fetal factors (BMI < 20 kg/m², primiparity [37], multiple pregnancies [21–23], male fetus

21 [19,24,25], history of AFLP [26]), and genetic and non-genetic factors altering mitochondrial

22 function [29,38–42]. Infants born from mothers with AFLP should be systematically screened

23 for mitochondrial fatty-acid oxidation deficiency to prevent metabolic decompensation.

1 Our study has several strengths. This study is the most extensive retrospective European study
2 on AFLP in the last decade. It provided detailed information on the clinical and biological
3 characteristics of patients with AFLP. It also gave reports on maternal and fetal prognosis.
4 However, it is a retrospective study, and the results might not be generalizable. The limited
5 number of patients reflects the low incidence of the disease and the impossibility of making a
6 multivariate analysis in our study. Two patients did not present six Swansea criteria but were
7 classified as AFLP after the exclusion of all other liver diseases of pregnancy. Finally, only
8 two out of 18 children were screened for fatty acid oxidation disorders, and only one of them
9 before clinical decompensation. Association between fatty acid oxidation disorders and AFLP
10 has been widely reported and, therefore, should have triggered neonatal testing in all cases.
11 However, as some contributors to the manuscript are regional referents following all LCHAD
12 deficiency-diagnosed infants in the geographic area, we note that, unfortunately, many
13 children are not tested.
14 In conclusion, we identified an incidence of 1/7,914 pregnancies of AFLP. Prolonged
15 maternal PT was associated with maternal complications. The term at birth correlated with
16 infant complications. Moreover, we point out the need for screening infants for mitochondrial
17 beta-oxidation of fatty acid disorders to limit the risk of infant deaths, when the mother
18 developed AFPL during pregnancy.

19
20

1 **TABLE LEGENDS**

2

3 **Table 1: Mother's baseline characteristics, biological data at diagnosis for women**

4 **Table 2: Patients outcomes and treatments**

5 DIC: disseminated intravascular coagulopathy

6 Acute kidney failure: Creatinine > 100 µmol/L

7 Hepatocellular insufficiency: cytolysis > 2N, bilirubin > 14 µmol/L, PT < 70 % and **Factor 5**

8 < 70 %

9 **Table 3: Univariate analysis of the risk factors of severe complications in AFLP**

10 **(maternal and neonatal)**

11 All variables with a p-value < 0.10 are presented. For this analysis, the mother with twin

12 gestation was excluded, so 17 pregnancies were studied. In bold, are indicated *p* values <

13 0.05.

14 **Supplementary Table 1: Primary published studies on AFLP cohorts over the last**

15 **decade**

16

17

1 **FIGURE LEGENDS**

2

3 **Figure 1: Flow chart of patients' selection**

4 n = number, AFLP = Acute Fatty Liver of Pregnancy, HELLP = Hemolysis, Elevated Liver
5 enzymes, and Low Platelet count syndrome

6

7

8 **Figure 2:**

9 **A. Swansea criteria in the study population [7] and clinical signs at diagnosis of**

10 **AFLP.** Criteria were divided into four different classes, namely clinical, biological,
11 imaging, and pathology. Other symptoms were listed. AST = aspartate
12 aminotransferase, ALT = alanine aminotransferase

13 **B. Number of patients fulfilling the Swansea criteria**

14

1 **DISCLOSURE OF ANY SOURCE OF FINANCIAL SUPPORT OF THE STUDY:** The
2 authors have no disclosures to declare. We did not get any funding for this project.

3
4 **SHORT TITLE: Prognosis factors in acute fatty liver of pregnancy**

5
6 **ACKNOWLEDGMENTS**
7 The authors are grateful to all the physicians and biologists involved in the data collection.

8
9 **AUTHOR CONTRIBUTIONS**

10 YJ, KP, CM designed and performed the research, analyzed the data, wrote and revised the
11 manuscript. ML, GB, CR, EP, EB-J, CB, BF, VL analyzed the data and revised the
12 manuscript.

13
14 **PRECIS:** In the acute fatty liver of pregnancy, maternal and infant outcomes are associated
15 with prothrombin time and weeks of gestation at delivery, respectively.

16
17

1 Table 1: Mother's baseline characteristics, biological data at diagnosis for women

2

	Min-max	Median (IQ) n	Reference values for the third trimester of pregnancy
Mother's baseline characteristics			
Maternal age (year)	17-39	27.5 (IQ 26-29.8)	
Body mass index (BMI) (kg/m ²) BMI < 19 kg/m ²	17 - 27	21.5 (IQ 20.3-24.9) n=3	
Gestational age at diagnosis (WG)	28-39	35.2 (IQ 33.1-37.9)	
Parity 0 1 2	0-2	n = 11 n = 5 n = 2	
Hematological data			
Hemoglobin (g/dL)	10.8-16.9	13.2 (IQ 12.4-15.1)	11-12
Leukocytes (10 ⁹ /L)	7.6-26.3	14.9 (IQ 11.9-21)	4-15
Platelets (10 ⁹ /L)	44-347	175 (IQ 154 -227)	150-400
Prothombin Ratio (%)	18-97	44.5 (IQ 31-62)	80-100
Fibrinogen (g/L)	0.57-6.34	2.3 (IQ 1.8-2.86)	5-6
Factor 5 (%)	21-69	43 (IQ 27-49)	70-120
Biochemical data			
AST (U/L)	96-3486	438 (IQ 236-488)	0-35
ALT (U/L)	124-2148	463 (IQ 290-540)	0-35
ALP (U/L)	106-1302	340 (IQ 236-595)	30-120
GGT (U/L)	20-398	74 (IQ 51-231)	0-30
Total bilirubin (µmol/L)	26-206	67.5 (IQ 51-95)	2-12
LDH (U/L)	341-2680	824 (IQ 532-1092)	50-150
Creatinine (µmol/L)	41-280	150 (IQ 102-180)	35-71
Glomerular filtration rate (mL/min)	16-137	40 (IQ 33-66)	
Uric acid (µmol/L)	241-1197	578 (IQ 398-607)	120-420
Swansea criteria			
Six or more Swansea criteria	4-10	n=16	

3 WG = week of gestation, BMI = Body mass index IQ = interquartile, n = number , PT =
4 prothrombin time ratio, AST = aspartate aminotransferase, ALT = alanine aminotransferase,

- 1 ALP = alkaline phosphatase, GGT = gamma-glutamyl transferase, LDH = lactate
- 2 dehydrogenase

Accepted manuscript

1 Table 2: Patients outcomes and treatments

2

Maternal clinical features (n=18)	
Hospitalization in ICU	14 (78%)
Less than two days	9 (72%)
Two days or more	5 (28%)
Hemorrhage	3 (17%)
DIC	6 (33%)
Pleural effusion and or ascites	3 (17%)
Kidney failure	14 (78%)
Hepatocellular insufficiency	18 (100%)
Blood transfusion	6 (33%)
Plasma transfusion	8 (44%)
Fibrinogen transfusion	6 (33%)
Albumin transfusion	2 (11%)
Neonatal outcomes (n=19)	
Delivery at < 34 WG	5 (26%)
Delivery between 34 - 37 WG	8 (42%)
Intrauterine fetal distress	7 (37%)
Neonatal intensive care unit	10 (53%)
Birth weight < 2,000g	4 (21%)
Fetal death	2 (10.5%)
Infant death from complications	1 (5%)

3

4 ICU = intensive care unit, DIC = disseminated intravascular coagulation,

5 Acute kidney failure: Creatinine > 100 µmol/L

6 Hepatocellular insufficiency: cytolysis > 2N, bilirubin > 14 µmol/L , PT < 70 % and Factor 5
7 < 70 %

8

9

1 Table 3: Univariate analysis of the risk factors of severe complications in AFLP (maternal and
 2 neonatal) (n=17)
 3
 4
 5

	OR CI 95%	<i>p</i>
Maternal outcomes		
Swansea criteria	2.35 [0.92 ; 6.01]	<i>p</i> = 0.0733
Parity	10.00 [1.05 ; 95.46]	<i>p</i> = 0.0455
PT	0.86 [0.73 ; 1.00]	<i>p</i> = 0.0493
Neonatal outcomes		
GGT	0.99 [0.98 ; 1.00]	<i>p</i> = 0.0944
Uric acid *	1.01 [1.00 ; 1.03]	<i>p</i> = 0.0635
Gestational age at delivery	0.37 [0.14 ; 0.96]	<i>p</i> = 0.0417

6
 7 All variables with a *p*-value < 0.10 are presented. For this analysis, the mother with twin
 8 gestation was excluded, so 17 pregnancies were studied. In bold, are indicated *p* values <
 9 0.05.

10 OR = Odds Ratio, CI = Confidence Interval, PT = Prothombin Time ratio, GGT = gamma-
 11 glutamyl transferase
 12
 13
 14

Supplementary Table 1: Primary published studies on AFLP cohorts over the last decade

Reference	Nature of the study	Prevalence of AFLP	Diagnosis of AFLP	WG at diagnosis mean +/-SD	Main results
Chang <i>et al.</i> [18]	10.5-year retrospective and single-center	55/220	Clinical features and laboratory findings	36.26±2.58	<p>AFLP mothers were younger, with fewer pregnancies, complicated with more pregnancy-induced hypertension, twins, fetal growth restriction and male fetuses</p> <p>Severe negative outcomes for mothers (27.3% vs. 0.9%) and newborn asphyxia (24.6% vs.0.9%) were observed in AFLP population</p> <p>Patients with negative fetal outcomes were younger, had more singleton rates, increased mean value of ALT and T-Bilirubin, decreased prothrombin activity</p>
Lin <i>et al.</i> [43]	8-year retrospective and single-center	5/426 pregnant women ≥20 weeks of gestational age	NA	NA	<p>Pregnancy with acute fatty liver is a risk factor for ICU admission (OR=16.233)</p> <p>Acute fatty liver was statistically significant with pregnant women mortality (p<0.05)</p>
Gao <i>et al.</i> [17]	5-year retrospective and multicenter	133/140	Clinical features and laboratory findings and ≥6 Swansea criteria	36.1±2.7	<p>Maternal death: 68.2%</p> <p>50% of perinatal death</p> <p>Risk for poor maternal outcomes: male fetus, postpartum diagnosis of AFLP, intrauterine fetal death, DIC, prolonged PT and activated partial thromboplastin time</p> <p>Risk factors for fetal mortality: fetal distress, prolonged activated partial thromboplastin time</p>

Reference	Nature of the study	Prevalence of AFLP	Diagnosis of AFLP	WG at diagnosis mean +/-SD	Main results
Zhang <i>et al.</i> [20]	5-year retrospective study	56/56	Based on Swansea criteria and AFPL-triad of Vigil-de-Garcia and Montufar-Rueda	33.68±4.15	Risk factors for complications: PT and INR Risk factors for perinatal death: Gestational age at delivery, direct bilirubin, and fibrin degradation products Main maternal complications: hypoproteinemia, coagulopathy, acute renal failure, ascites, and DIC 16% of perinatal death
Allen <i>et al.</i> [44]	14-year retrospective and multicenter	1/35,101 pregnancies 247 women with liver disease of pregnancy	Clinical and biological diagnosis	NA	The infant of the AFLP mother died
Nelson <i>et al.</i> [6]	38-year retrospective and single-center	51/492,000 deliveries	Clinical and biological diagnosis Swansea criteria and AFPL-triad of Vigil-de-Garcia and Montufar-Rueda	37.0 ± 2.6	Risk factors for complications of AFLP: Hepatic failure with multiorgan involvement Maternal death: 4% Perinatal mortality rate 12% Incidence of 1/10,000 births
Vigil-de Gracia <i>et al.</i> [28]	14-year retrospective and multicenter	35/35	Clinical symptoms, complications, and laboratory evidence of acute hepatic dysfunction in the third trimester of pregnancy with complete resolution of the liver function postpartum	36	Maternal mortality: 11.4% Fetal mortality rate: 12.5%

Reference	Nature of the study	Prevalence of AFLP	Diagnosis of AFLP	WG at diagnosis mean +/-SD	Main results
Dekker <i>et al.</i> [45]	23-year retrospective and multicenter	6/4,608,253 live births 538 cases of maternal death	Clinical and biological diagnosis Microscopic examination of liver in post mortem: histological signs of AFLP	38.2	Maternal mortality: 0.13/100,000 live births Maternal morbidity: 3.2/100,000 deliveries Perinatal mortality rate: 22.7%
	2-year retrospective and multicenter	12/371,021 deliveries	Clinical and biological diagnosis	34.5	Incidence: 3.2/100,000 births
Lau <i>et al.</i> [31]	22-year retrospective and single-center	18/136,214 deliveries	acute hepatic failure in the 3 rd trimester, abdominal pain, nausea or vomiting, laboratory evidence of hepatic failure, signs of coagulopathy	35.6 ±2.8	Risk factors for complications: Morbidities: acute renal failure, hypoglycemia, DIC Maternal death: 11% Perinatal mortality rate: 18% Incidence: 1/7,568 births
Goel <i>et al.</i> [22]	8-year retrospective and single-center	24/34	Swansea criteria versus histological examination	36	20 patients fulfilled Swansea criteria for AFLP Sensitivity of Swansea criteria for microvesicular steatosis: 100% Specificity of Swansea criteria for microvesicular steatosis: 57%

Reference	Nature of the study	Prevalence of AFLP	Diagnosis of AFLP	WG at diagnosis mean +/-SD	Main results
Knight <i>et al.</i> [19]	20-month retrospective from 229 UK hospitals	57/80	Symptoms and signs consistent with AFLP or AFLP confirmed by biopsy or postmortem	Median 36	Risk factors for complications: Twin pregnancies and low BMI Maternal death: 1.8% Perinatal mortality rate: 10.4% Incidence of 1/20,000 births

AFLP = Acute Fatty Liver of Pregnancy, WG = Week of Gestation, SD = Standard Deviation, NA = Not Available, ICU = Intensive Care Unit, OR = Odds

Ratio, DIC = Disseminated Intravascular Coagulation, INR = International Normalized Ratio, BMI = Body Mass Index

REFERENCES

- [1] García-Romero CS, Guzman C, Cervantes A, Cerbón M. Liver disease in pregnancy: Medical aspects and their implications for mother and child. *Ann Hepatol* 2019;18:553–62.
- [2] Sheehan HL. The Pathology of Acute Yellow Atrophy and Delayed Chloroform Poisoning. *BJOG Int J Obstet Gynaecol* 1940;47:49–62.
- [3] Knox TA, Olans LB. Liver disease in pregnancy. *N Engl J Med* 1996;335:569–76..
- [4] Ibdah J-A. Acute fatty liver of pregnancy: an update on pathogenesis and clinical implications. *World J Gastroenterol* 2006;12:7397–404.
- [5] Ahmed KT, Almashhrawi AA, Rahman RN, Hammoud GM, Ibdah JA. Liver diseases in pregnancy: diseases unique to pregnancy. *World J Gastroenterol* 2013;19:7639–46.
- [6] Nelson DB, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: clinical outcomes and expected duration of recovery. *Am J Obstet Gynecol* 2013;209:456.e1-7.
- [7] Ch'ng CL, Morgan M, Hainsworth I, Kingham JGC. Prospective study of liver dysfunction in pregnancy in Southwest Wales. *Gut* 2002;51:876–80.
- [8] Goel A, Jamwal KD, Ramachandran A, Balasubramanian KA, Eapen CE. Pregnancy-related liver disorders. *J Clin Exp Hepatol* 2014;4:151–62.
- [9] Liu J, Ghaziani TT, Wolf JL. Acute Fatty Liver Disease of Pregnancy: Updates in Pathogenesis, Diagnosis, and Management. *Am J Gastroenterol* 2017;112:838–46.
- [10] Fromenty B, Pessayre D. Inhibition of mitochondrial beta-oxidation as a mechanism of hepatotoxicity. *Pharmacol Ther* 1995;67:101–54.
- [11] Missiroli S, Genovese I, Perrone M, Vezzani B, Vitto VAM, Giorgi C. The Role of Mitochondria in Inflammation: From Cancer to Neurodegenerative Disorders. *J Clin Med* 2020;9:740.
- [12] Ibdah JA, Bennett MJ, Rinaldo P, Zhao Y, Gibson B, Sims HF, et al. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. *N Engl J Med* 1999;340:1723–31.
- [13] Yang Z, Yamada J, Zhao Y, Strauss AW, Ibdah JA. Prospective screening for pediatric mitochondrial trifunctional protein defects in pregnancies complicated by liver disease. *JAMA* 2002;288:2163–6.
- [14] Browning MF, Levy HL, Wilkins-Haug LE, Larson C, Shih VE. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. *Obstet Gynecol* 2006;107:115–20. <https://doi.org/10.1097/01.AOG.0000191297.47183.bd>.
- [15] Natarajan SK, Ibdah JA. Role of 3-Hydroxy Fatty Acid-Induced Hepatic Lipotoxicity in Acute Fatty Liver of Pregnancy. *Int J Mol Sci* 2018;19.
- [16] Ibdah JA, Yang Z, Bennett MJ. Liver disease in pregnancy and fetal fatty acid oxidation defects. *Mol Genet Metab* 2000;71:182–9.
- [17] Gao Q, Qu X, Chen X, Zhang J, Liu F, Tian S, et al. Outcomes and risk factors of patients with acute fatty liver of pregnancy: a multicentre retrospective study. *Singapore Med J* 2018;59:425–30.
- [18] Chang L, Wang M, Liu H, Meng Q, Yu H, Wu Y-M, et al. Pregnancy outcomes of patients with acute fatty liver of pregnancy: a case control study. *BMC Pregnancy Childbirth* 2020;20:282.
- [19] Knight M, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P, UK Obstetric Surveillance System. A prospective national study of acute fatty liver of pregnancy in the UK. *Gut* 2008;57:951–6.

- [20] Zhang Y-P, Kong W-Q, Zhou S-P, Gong Y-H, Zhou R. Acute Fatty Liver of Pregnancy: A Retrospective Analysis of 56 Cases. *Chin Med J (Engl)* 2016;129:1208–14.
- [21] Reyes H, Sandoval L, Wainstein A, Ribalta J, Donoso S, Smok G, et al. Acute fatty liver of pregnancy: a clinical study of 12 episodes in 11 patients. *Gut* 1994;35:101.
- [22] Goel A, Ramakrishna B, Zachariah U, Ramachandran J, Eapen CE, Kurian G, et al. How accurate are the Swansea criteria to diagnose acute fatty liver of pregnancy in predicting hepatic microvesicular steatosis? *Gut* 2011;60:138–9; author reply 139-140.
- [23] Meng J, Wang S, Gu Y, Lv H, Jiang J, Wang X. Prenatal predictors in postpartum recovery for acute fatty liver of pregnancy: experiences at a tertiary referral center. *Arch Gynecol Obstet* 2016;293:1185–91.
- [24] Cheng N, Xiang T, Wu X, Li M, Xie Y, Zhang L. Acute fatty liver of pregnancy: a retrospective study of 32 cases in South China. *J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet* 2014;27:1693–7.
- [25] Treem WR, Shoup ME, Hale DE, Bennett MJ, Rinaldo P, Millington DS, et al. Acute fatty liver of pregnancy, hemolysis, elevated liver enzymes, and low platelets syndrome, and long chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. *Am J Gastroenterol* 1996;91:2293–300.
- [26] Bacq Y. Liver diseases unique to pregnancy: a 2010 update. *Clin Res Hepatol Gastroenterol* 2011;35:182–93.
- [27] Wei Q, Zhang L, Liu X. Clinical diagnosis and treatment of acute fatty liver of pregnancy: a literature review and 11 new cases. *J Obstet Gynaecol Res* 2010;36:751–6.
- [28] Vigil-de Gracia P, Montufar-Rueda C. Acute fatty liver of pregnancy: diagnosis, treatment, and outcome based on 35 consecutive cases. *J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet* 2011;24:1143–6.
- [29] Morton A. Presumed acute fatty liver of pregnancy following influenza A hepatitis. *Obstet Med* 2017;10:186–8.
- [30] Mellouli MM, Amara FB, Maghrebi H, Bouchnack M, Khaled N, Rezigia H. Acute fatty liver of pregnancy over a 10-year period at a Tunisian tertiary care center. *Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet* 2012;117:88–9.
- [31] Lau H-H, Chen Y-Y, Huang J-P, Chen C-Y, Su T-H, Chen C-P. Acute fatty liver of pregnancy in a Taiwanese tertiary care center: a retrospective review. *Taiwan J Obstet Gynecol* 2010;49:156–9.
- [32] Bernuau J, Degott C, Nouel O, Rueff B, Benhamou JP. Non-fatal acute fatty liver of pregnancy. *Gut* 1983;24:340–4.
- [33] Sibai BM. Imitators of severe preeclampsia. *Obstet Gynecol* 2007;109:956–66.
- [34] Hay JE. Liver disease in pregnancy. *Hepatology* 2008;47:1067–76.
- [35] Gao H-Z, Kobayashi K, Tabata A, Tsuge H, Iijima M, Yasuda T, et al. Identification of 16 novel mutations in the argininosuccinate synthetase gene and genotype-phenotype correlation in 38 classical citrullinemia patients. *Hum Mutat* 2003;22:24–34.
- [36] Maitra A, Domiati-Saad R, Yost N, Cunningham G, Rogers BB, Bennett MJ. Absence of the G1528C (E474Q) mutation in the alpha-subunit of the mitochondrial trifunctional protein in women with acute fatty liver of pregnancy. *Pediatr Res* 2002;51:658–61.
- [37] Zhou G, Zhang X, Ge S. Retrospective analysis of acute fatty liver of pregnancy: twenty-eight cases and discussion of anesthesia. *Gynecol Obstet Invest* 2013;76:83–9.
- [38] Mansouri A, Fromenty B, Durand F, Degott C, Bernuau J, Pessayre D. Assessment of the prevalence of genetic metabolic defects in acute fatty liver of pregnancy. *J Hepatol* 1996;25:781.

- [39] Grimbert S, Fisch C, Deschamps D, Berson A, Fromenty B, Feldmann G, et al. Effects of female sex hormones on mitochondria: possible role in acute fatty liver of pregnancy. *Am J Physiol* 1995;268:G107-115.
- [40] Lamprecht A, Morton A, Laurie J, Lee W. Acute fatty liver of pregnancy and concomitant medical conditions: A review of cases at a quaternary obstetric hospital. *Obstet Med* 2018;11:178–81.
- [41] Anon B, Barbet C, Gendrot C, Labarthe F, Bacq Y. [Acute fatty liver of pregnancy and mitochondrial fatty acid oxidation. Consequences for the offspring]. *Arch Pediatr Organe Off Soc Francaise Pediatr* 2017.
- [42] Kong X-F, Zhang X-X, Yu Y-Y, Shi Q, La D-D, Zhu-Ge C-D, et al. No mutation was found in the alpha-subunit of the mitochondrial tri-functional protein in one patient with severe acute fatty liver of pregnancy and her relatives. *J Gastroenterol Hepatol* 2007;22:2107–11.
- [43] Lin L, Chen Y-H, Sun W, Gong J-J, Li P, Chen J-J, et al. Risk factors of obstetric admissions to the intensive care unit: An 8-year retrospective study. *Medicine (Baltimore)* 2019;98:e14835.
- [44] Allen AM, Kim WR, Larson JJ, Rosedahl JK, Yawn BP, McKeon K, et al. The Epidemiology of Liver Diseases Unique to Pregnancy in a US Community: A Population-Based Study. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* 2016;14:287-294.e1-2.
- [45] Dekker RR, Schutte JM, Stekelenburg J, Zwart JJ, van Roosmalen J. Maternal mortality and severe maternal morbidity from acute fatty liver of pregnancy in the Netherlands. *Eur J Obstet Gynecol Reprod Biol* 2011;157:27–31.

- We analyzed acute fatty liver of pregnancy in a large multicenter cohort
- Incidence of AFLP was estimated as one case for 7914 pregnancies.
- Increased prothrombin time is a risk factor of maternal complications.
- Infants born to mothers with ALFP should be screened for β -oxidation deficiency.

Accepted manuscript