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[Review ARTICLE] for *J Obstet Gynaecol Res*

**Differentiation of acute fatty liver of pregnancy from syndrome of hemolysis,
elevated liver enzymes, and low platelet counts**

Short title: AFLP and HELLP syndrome

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21 ABSTRACT

22 **Background:** As proposed criteria (Swansea criteria) for the diagnosis of acute fatty
23 liver of pregnancy (AFLP) do not include antithrombin activity, diagnosis of AFLP may
24 be delayed.

25 **Aims:** To underscore problems in differential diagnosis of AFLP and the syndrome of
26 hemolysis, elevated liver enzymes, and low platelet counts (HELLP syndrome) and to
27 facilitate prompt diagnosis of AFLP.

28 **Methods:** Review of literatures dealing with liver dysfunction in pregnancy, HELLP
29 syndrome, and AFLP.

30 **Results:** AFLP and HELLP syndrome shared common clinical, laboratory, histological,
31 and genetic features, differential diagnosis between them was often difficult. However,
32 HELLP syndrome was likely to occur in patients with hypertension, but AFLP occurred
33 often in the absence of hypertension. In addition, AFLP was exclusively associated with
34 pregnancy-induced antithrombin deficiency (PIATD). Approximately 50% of patients
35 with AFLP did not have thrombocytopenia at presentation. As the Swansea criteria for
36 AFLP did not include PIATD, diagnosis of AFLP was delayed until manifestation of
37 life-threatening complications; 60 percent of women were admitted to intensive care
38 and 15% to a specialist liver unit.

39 **Conclusions:** Incorporation of AT activity $< 65\%$ into the diagnostic criteria for AFLP
40 may facilitate suspicion and prompt diagnosis of AFLP, decrease uncertainty regarding
41 the diagnosis of AFLP, and contribute to better investigation and understanding of the
42 process leading to the development of liver dysfunction.

AFLP and HELLP syndrome

43 **Key words:** antithrombin activity, blood vessel permeability, liver dysfunction,
44 preeclampsia, thrombocytopenia

45

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Introduction

Approximately 3% of pregnant women develop liver dysfunction [1]. Acute fatty liver of pregnancy (AFLP) and the syndrome of hemolysis, elevated liver enzymes, and low platelet counts (HELLP syndrome) are life-threatening complications with high rates of severe maternal morbidity and mortality [2 – 4]. However, there has been a great deal of confusion regarding the differential diagnosis between AFLP and HELLP syndrome. The former is a disease entity based on liver histology originally derived from autopsy findings by Sheehan in 1940 [5], while the latter is a disease entity based on laboratory data (LDH elevation, AST elevation, and thrombocytopenia) established in 1982 by Weinstein [6]. As both conditions require termination of pregnancy to rescue the mother, early suspicion and prompt diagnosis may be important to improve outcome.

This review was conducted to underscore the problems in differential diagnosis of AFLP from HELLP syndrome, facilitate suspicion and prompt diagnosis of AFLP, and to decrease uncertainty regarding the diagnosis of AFLP.

Methods

Clinical symptoms, and laboratory, histological, and genetic features suggestive of AFLP and HELLP syndrome were studied in English literature reports that were abstracted from the database of PubMed (1979 – December 2012) using the search terms including “acute fatty liver of pregnancy”, “HELLP syndrome”, and “liver

dysfunction in pregnancy”. English literatures cited in these reports were also reviewed.

Results and Discussion

Symptoms and complications in AFLP and HELLP syndrome and Swansea criteria for diagnosis of AFLP

Prodromal symptoms of AFLP **included** nausea and vomiting, abdominal pain, malaise, polydipsia/polyuria, jaundice/dark urine, encephalopathy, and hypertension/preeclampsia [7 – 13] (Table 1). Similar symptoms were seen in HELLP syndrome: malaise in 100% [6]; nausea with or without vomiting in 24% – 100% [6, 14, 15]; and abdominal pain in 31% – 90% of cases [6, 14, 15]. Although hypertension **was** seen less frequently in AFLP (26% – 70% [Table 1] vs. 80% – 100% in HELLP syndrome [6, 14, 15]), severe morbidities such as acute renal failure, coagulopathy, and encephalopathy **appeared** to be more frequent in AFLP than in HELLP syndrome (Table 1). Acute renal failure, coagulopathy, and central nervous system involvement **occurred** in 1.2% – 8.0%, 20% – 38%, and 2.4% of HELLP syndrome cases, respectively [14, 15]. Thus, **as AFLP and HELLP syndrome shared common clinical symptoms, differential diagnosis between them was often difficult.**

As women with AFLP often **lacked** hypertension, they may **not have been** found to have AFLP until they manifest clinical symptoms. As women with preeclampsia are recommended to undergo blood tests at least twice a week [16], laboratory

abnormalities may be found early before the development of serious complications in HELLP syndrome. These observations may explain why women with severe hypertension are less likely to show severe thrombocytopenia in HELLP syndrome [17].

Criteria for diagnosis of AFLP have been proposed (Table 2) [1,11]. These allowed diagnosis of AFLP when women were critically ill, but approximately half of AFLP patients based on the Swansea criteria also fulfilled the criteria for HELLP syndrome [18]. Of the 57 confirmed cases with AFLP based on the Swansea criteria, including 10 women with twins [11], 84% of women indeed exhibited clinical symptoms: vomiting (60%), abdominal pain (56%), polydipsia (12%) and encephalopathy (9%). Sixty percent of women were admitted to intensive care and 15% to a specialist liver unit. One woman received a liver transplant. One woman died. There were seven deaths among 67 infants [11]. Thus, the Swansea criteria [1, 11] may allow diagnosis of AFLP only when women become critically ill.

Liver histology in patients with AFLP and HELLP syndrome

The current clinical entity of AFLP was established by Sheehan in 1940 [5]. Liver histology of AFLP differed from “true acute yellow atrophy of liver” in which liver cell necrosis was the main finding, while there were gross fatty changes affecting the entire lobule except a sharply defined rim of normal cells around the portal tracts [5]. Since then, microvesicular fatty change in the liver has been considered characteristic for AFLP [19,20]. However, as fatty changes were seen to varying degrees in patients with

either AFLP or HELLP syndrome [21 – 23], and in pregnant women without liver dysfunction [21] and non-pregnant women [24], detection of fatty changes in the liver **was** not diagnostic of AFLP. Other findings such as fibrin deposition and focal parenchymal necrosis in the liver **overlapped** between AFLP and HELLP syndrome [22, 25]. **Thus, as AFLP and HELLP syndrome shared common histological features, differential diagnosis between them was often difficult.**

Genetic background in pregnant women with liver dysfunction

An association between maternal liver dysfunction and recessively inherited fatty acid oxidation (FAO) disorders in the fetus has been elucidated in the past two decades [26 – 30]. Mitochondrial trifunctional protein (MTP) catalyzes the last three steps in mitochondrial long-chain FAO. Human defects in the MTP complex **caused** either isolated long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency or complete MTP deficiency with markedly reduced FAO activity [31]. Women carrying fetuses with MTP defects **were** at higher risk of developing liver dysfunction, including AFLP and HELLP syndrome [28 – 30]. A prospective study focusing on the association between maternal liver dysfunction and fetal MTP mutations demonstrated that 5 of 20 pregnancies affected by AFLP carried a fetus with LCHAD deficiency, while none of 81 pregnancies affected by HELLP syndrome carried a fetus with LCHAD deficiency [30]. However, as the majority of women complicated with AFLP did not carry a fetus with MTP mutations, it **is still** unclear whether these tests are clinically useful for the differential diagnosis of AFLP from HELLP syndrome.

Platelet count and AT activity in patients with AFLP and HELLP syndrome

Platelets are essential for hemostasis and its count ranges from $150 \times 10^9/L$ to $350 \times 10^9/L$ in healthy subjects. Antithrombin (AT) is essential for the anticoagulation of circulating blood and its activity ranges from 80% to 130% in healthy subjects.

Thrombocytopenia is **exclusively** seen in HELLP syndrome [6], while varied platelet counts were seen in AFLP [3, 32 – 39, 9, 11 – 13, 40 – 48] (Table 3). The mean or median value for platelet count at presentation **ranged** from $123 \times 10^9/L$ [42] to $151 \times 10^9/L$ [45], while AT activity **was** exclusively and severely depressed, ranging from 0.0% to 69% when tested [32 – 39] (Table 3). However, two prospective studies to determine the incidences of liver dysfunction and AFLP conducted in the UK in 1999 and 2005 using the Swansea criteria for diagnosis of AFLP (Table 2) did not determine AT activity or query status of AT activity [1,11]. Twenty-four (52%) of 46 AFLP patients tested had coagulopathy in the absence of thrombocytopenia ($< 100 \times 10^9/L$) [11].

Changes in platelet count and AT activity during pregnancy

Both production and consumption of platelets **were** enhanced in pregnancy [49 – 51] especially in women with preeclampsia [49,52]. Hypermegakaryocytosis **was** seen in pregnant rats [53]. Approximately 6.0% of pregnant women showed reduced peripartum

platelet count $< 150 \times 10^9/L$ [54 – 56]. Of 1027 women with a reduced platelet count, 216 (21%) were explained by pregnancy-induced hypertension (PIH), and 756 (74%) were not explained by known disorders, such as autoimmune thrombocytopenic purpura or systemic lupus erythematosus [55], yielding the new term “gestational thrombocytopenia” [57]. Gestational thrombocytopenia was shown to be due to a gradual decline in the platelet count during the third trimester of pregnancy [56].

Reduced AT activity was seen in preeclampsia [58]. AT activity decreased even in healthy women during the third trimester; AT activity decreased significantly from $100\% \pm 12\%$ at 28 weeks of gestation to $82\% \pm 8\%$ at 36 weeks of gestation in women with AT activity $< 91\%$ at 36 weeks of gestation [59]; and 1st and 3rd percentile AT activity values were 66% and 69%, respectively, just before birth in healthy women [60].

Relationships between the decrease in the platelet count and AT activity and subsequent aspartate aminotransferase (AST) elevation

The relation between gestational thrombocytopenia and HELLP syndrome was examined in women with singleton pregnancies [61]. The frequency of perinatal AST elevation (> 30 IU/L) was compared between 24 women with gestational thrombocytopenia and 213 control women. The 24 women exhibited a gradual decline in platelet count from $210 \pm 31 \times 10^9/L$ at the beginning of pregnancy to $127 \pm 24 \times 10^9/L$ before delivery. AST elevation occurred more frequently in the women with gestational thrombocytopenia than in the controls (21% [5/24] vs. 2.8% [6/213], respectively, $P <$

0.001). This relationship was verified again in twin pregnancies [62]. Thus, women with gestational thrombocytopenia were at higher risk of developing liver dysfunction (Fig. 1).

In patients with liver dysfunction whose antenatal changes in AT activity were documented, AT activity gradually decreased to < 65% before the development of liver dysfunction [25, 36, 38,]. These cases strongly suggested that women with reduced AT activity were at higher risk of developing liver dysfunction. This hypothesis was verified in a longitudinal and observational study of 237 women with twin pregnancies [62]. The risk of AST elevation increased as the antenatal AT activity and/or the platelet count decreased and was associated more closely with AT activity than the platelet count [62], yielding the new term “pregnancy-induced AT deficiency (PIATD)” [63,64]. Thus, women with PIATD were at higher risk of developing liver dysfunction (Fig. 1).

Women with PIATD alone accounted for a considerable fraction of those with liver dysfunction. In a study of 13 hospitalized women with liver dysfunction [25], 7 had thrombocytopenia ($< 130 \times 10^9/L$) on admission and one of the remaining 6 developed thrombocytopenia. AT activity was determined in 12 patients; PIATD (AT activity < 65%) alone in 2, both PIATD and thrombocytopenia in 5, thrombocytopenia alone in 3, and neither PIATD nor thrombocytopenia in 2 [25]. In another study [65], 6 women with AT activity < 45% exclusively developed AST elevation (> 60 IU/L), but 5 of the 6 did not develop thrombocytopenia ($< 150 \times 10^9/L$), while none of 144 women with AT activity $\geq 45\%$, including 9 women with thrombocytopenia, developed AST elevation

[65]. However, both thrombocytopenia and PIATD **occurred** in advanced stage; in 18 women diagnosed with HELLP syndrome, platelet count (mean and [range]) of 83 (15 – 131)×10⁹/L and AT activity of 60 (18 – 98)% at admission decreased to 65 (20 – 97)×10⁹/L and 56 (18 – 95)% at delivery, respectively [66].

Reason for higher risk of developing HELLP syndrome and AFLP in multifetal pregnancies

The risk of HELLP syndrome **increased** with increasing number of fetuses; HELLP syndrome occurred in 0.2%, 0.9%, and 2.1% of singleton, twin, and triplet pregnancies, respectively [67]. A similar prevalence of HELLP syndrome, 1.4% (34/2478), was reported among women with twin pregnancies [68]. In other studies, HELLP syndrome occurred in 3.0% of twin pregnancies [62] and in 9.0% – 10.5% of triplet pregnancies [69,70]. Although twin pregnancies **accounted** for only 1.0% – 2.0% of all pregnancies, they accounted for 10.3% – 15.5% of all women with HELLP syndrome [14,71]. The platelet count **was** likely to decrease during pregnancy with increasing number of fetuses. The mean platelet count decreases gradually in women with twin and triplet pregnancies [59,62,72]. The 10th percentile value of platelet count before delivery, 137×10⁹/L [62] for twin pregnancies **corresponded** to 3rd – 4th percentile value for singleton pregnancies [54 – 56]. Gestational thrombocytopenia < 100×10⁹/L was seen in 17% of twin pregnancies [72] and in 17% – 43% triplet pregnancies [72,73]. As women with gestational thrombocytopenia are likely to develop liver dysfunction [61,62], multifetal pregnancies may be prone to HELLP syndrome.

223

224 The risk of AFLP was higher in twin than singleton pregnancies (Table 4). Among 16
225 reports of 10 or more women with AFLP, 12 reports indicated a high prevalence of twin
226 pregnancies ranging from 7.1% to 28.6% (Table 4). In another study, AFLP occurred in
227 7.3% of 55 women with triplet pregnancies [69]. Approximately 1.0% of women with
228 singleton pregnancies **showed** a gradual decline in AT activity to less than 65% in the
229 absence of hypertension [60,64]. In women with twin pregnancies, the mean AT activity
230 **decreased** gradually independent of hypertension [59,62]. The 10th percentile AT
231 activity value before delivery of 67% [62] for twin pregnancies **corresponded** to 2nd
232 percentile AT activity value for singleton pregnancies [60]. PIATD < 60% was present
233 in 17% and 57% of twin and triplet pregnancies, respectively [72]. As women with
234 PIATD are likely to develop liver dysfunction [36,38, 25,62], multifetal pregnancies
235 may be prone to AFLP.

236

237 *Clinical features of women with PIATD with or without liver dysfunction*

238 A considerable number of women with AFLP **showed** proteinuria in the absence of
239 hypertension [7,19,74], and **experienced** polydipsia and pulmonary edema (Table 1).
240 Reduced AT activity < 70% of that in controls **was** seen in approximately one third of
241 women with isolated proteinuria without PIH [75], suggesting a close relationship
242 between reduced AT activity and proteinuria. The appearance of pulmonary edema **may**
243 **be** likely a consequence of enhanced vascular permeability and the endothelial leakage
244 of plasma into the interstitial space. The plasma volume **was** reduced by approximately

20% in women with preeclampsia [76] in whom generalized edema was often seen [77]. The process underlying the retention of water during pregnancy may be reversed by parturition, and the excess water in the interstitial space may return into the intravascular space, resulting in a drop in the hematocrit value; the excess water may be then excreted as urine. Women with PIATD showed a larger and sustained decrease in the hematocrit value after delivery than those without PIATD, suggesting antenatal hemoconcentration and a decreased plasma volume in women with PIATD [64]. AT escaped from the blood into the interstitial space [78]; six ascites samples from six women with PIATD and generalized edema contained AT (mean $\pm$ SD, 4.9 ± 2.2 mg/dL; range, 2.7 – 8.8 mg/dL) and exhibited an AT activity level of $15.5\% \pm 6.0\%$ (range, 10% – 24%) (reference intervals in the blood, 17.0 – 25.0 mg/dL for concentration and 80% – 130% for activity). These findings suggested that AT activity may have reflected the degree of vascular permeability and resultant shortage of circulating plasma volume, explaining higher rates of pre-renal acute renal failure (Table 1), decreased blood flow to the liver prior to the development of liver dysfunction [79], decreased blood flow in the celiac axis [35], and an antenatal high hemoglobin concentration in patients with severely depressed AT activity and liver dysfunction [65]. Hyperuricemia, frequently seen in patients with PIATD [64], AFLP [21, 36], and preeclampsia [80] may be explained by the reduced circulating plasma volume.

Conclusions and proposal for differentiation of AFLP from HELLP syndrome

Cardinal pathology associated with AFLP may be enhanced vascular permeability due

to endothelial cell dysfunction and resultant insufficiency in circulating blood volume and enhancement of coagulation-fibrinolysis leading to consumption coagulopathy. Clinical symptoms, such as vomiting and abdominal pain, were less likely to appear until AT activity was severely depressed to < 45% [65]. However, subtle changes associated with enhanced vascular permeability, such as edema, thirst/polydipsia, proteinuria, and excessive weight gain, may occur before AT activity is severely depressed [81]. Determination of AT activity in such women with the above minor symptoms and multifetal pregnancies may contribute to early suspicion or diagnosis of AFLP, thereby avoiding serious complications such as coagulopathy, renal failure, encephalopathy, and hepatic failure. AFLP requires liver transplantation in some women and may still be fatal in young women [3,4]. Incorporation of AT activity < 65% into the diagnostic criteria for AFLP (Fig. 2) may facilitate prompt diagnosis of AFLP, decrease uncertainty regarding the diagnosis of AFLP, and contribute to better investigation and understanding of the process leading to the development of liver dysfunction.

Conflicts of Interest

None of the authors have any conflicts of interest to declare

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Figure legend

Fig. 1: Schematic representation of the chronological relationship between decrease in AT activity and elevation of serum AST (aspartate aminotransferase) and LDH (lactate dehydrogenase)

Pregnancy-induced AT deficiency precedes elevation of the serum AST and LDH levels in women with AFLP. The reduced AT activity and elevated AST/LDH levels begin to normalize promptly after delivery if delivery occurs in timely manner before onset of coagulopathy.

Fig. 2: Proposal of flow-chart leading to early diagnosis of acute fatty liver of pregnancy (AFLP) and HELLP syndrome

The risk of AFLP and HELLP syndrome is higher in women with symptoms such as abdominal pain and polydipsia, pregnancy-induced hypertension, isolated proteinuria, and/or multifetal pregnancies than in women without these characteristics. *, Repeated blood test is advisable for women with either a reduced platelet count (but, not reaching $< 120 \times 10^9/L$) or reduced AT activity (but, not reaching $< 65\%$).

AT, antithrombin; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

Table 1. Frequency of symptoms and complications in women with AFLP

Symptoms/complications	% of women with AFLP [Reference]
Symptoms	
Nausea and vomiting	50% [12], 60% [11], 70% [9], 71% [8], 79% [13], 82% [7]
Abdominal pain	32% [13], 50% [8, 12], 55% [7], 56%[11], 70% [9]
Malaise	40% [9], 64% [8], 78%[12]
Polydipsia/polyuria	11% [13], 12% [11], 50% [9], 82%[7]
Jaundice/dark urine	29% [8], 32% [13], 94%[12], 100% [7, 9, 10]
Encephalopathy	9% [11], 11% [12, 13], 21% [8], 30% [9], 50% [37], 57%[10], 91%[7]
Hypertension/preeclampsia	26% [13], 32% [11], 36% [10], 39%[8], 70% [37]
Complications	
Acute renal failure	14% [11], 45% [7], 50% [10], 60% [9], 63%[13], 83% [12], 90%[37]
Postpartum hemorrhage	11% [13], 33% [12], 50% [9], 57%[10]
Coagulopathy	36%[7], 42% [11], 50%[9], 58% [13], 61% [12], 64% [10], 70% [37]
Pulmonary edema	5% [13], 7% [11], 17% [12], 30% [9]
Gastrointestinal bleeding	5%[13], 7% [8], 11% [12], 36%[10]

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Table 2. Swansea criteria for diagnosis of AFLP [1]

Six or more of the following features in the absence of another explanation

- Vomiting
 - Abdominal pain
 - Polydipsia/polyuria
 - Encephalopathy
 - Elevated bilirubin (> 14 mmol/L)
 - Hypoglycemia (< 4 mmol/L)
 - Elevated urate (> 340 mmol/L)
 - Leucocytosis ($> 11 \times 10^9$ /L)
 - Ascites or bright liver on ultrasound scan
 - Elevated transaminases (AST or ALT > 42 IU/L)
 - Elevated ammonia (> 47 mmol/L)
 - Renal impairment (creatinine > 150 mmol/L)
 - Coagulopathy (prothrombin time > 14 s or activated partial thromboplastin time > 34 s)
 - Microvesicular steatosis on liver biopsy
-

Figures in parentheses were used in the UK National Survey on AFLP [11]

Table 3. Antithrombin activity and platelet count in women with AFLP

Author (year) [Ref.]	Number of cases	Antithrombin (%, activity)	Platelet ($\times 10^9/L$)
Minakami et al. (1982)[32]	1	2.2 mg/dL [†]	136*
Mosvold et al. (1982) [33]	2	9.0%, 14%	75*, 201*
Hellgren et al. (1983)[34]	1	<10%	60*
Mabie (1992) [40]	1	NA	132¶
Usta et al. (1994)[41]	14	NA	126 [15 – 300] §
Matsuda (1994)[35]	1	5.0%	152*
Castro et al. (1996)[36]	23	11% [0% – 30%]	113 (11 – 186) §
Pereira et al. (1997)[42]	32	NA	123 (26 – 262) *
Vigil-De Gracia et al. (2001)[37]	10	30% [12% – 69%]	76 (21 – 179) §
Izumi et al. (1998)[38]	1	55%	180¶
Davidson et al. (1998)[43]	3	NA	WNR in 2*, 128 in 1*
Moldenhauer et al. (2004)[44]	12	NA	84 (28 – 176) ‡
Fesenmeier et al. (2005)[45]	16	NA	151 (33 – 303) ¶
Mjahed et al. (2006)[9]	10	NA	141 (40 – 240) *
Knight et al. (2008)[11]	57	NA	122 (14 – 436) §
Westbrook et al. (2010)[46]	18	NA	100 (33 – 180) §
Lau et al. (2010)[12]	18	NA	121 (13 – 219) *
Wei et al. (2010)[47]	11	NA	59 (40 – 126) §
Aso et al. (2010)[39]	2	15%, 28%	WNR in all 2*
Dekker et al. (2011)[3]	16	NA	WNR in 6 §
Mellouli (2012)[13]	19	NA	<100 in 9 cases §
Dey et al. (2012)[48]	1	NA	130¶

NA, not assessed; WNR, within normal range; [†], 17 – 25 mg/dL for normal reference value; *, on admission; ‡, nadir of platelet count; ¶, at diagnosis; §, at unspecified time.

Table 4. Frequency of twin pregnancy among women with AFLP

Author (year [Ref.])	No. of twins (%)
Reyes et al. (1994 [7])	0/11 (0.0)
Usta et al. (1994 [41])	0/14 (0.0)
Chen et al. (2008 [10])	0/14 (0.0)
Wei et al. (2010 [47])	0/11 (0.0)
Castro et al. (1996 [36])	2/28 (7.1)
Pereira et al. (1997 [42])	5/46* (10.9)
Vigil-De Gracia et al. (2001 [37])	4†/35 (11.0)
Riely (1987 [20])	19/140 (13.6)
Mellouli et al. (2011 [13])	3/19 (15.8)
Knight et al. (2008 [11])	10/57 (17.5)
Fesenmeier et al. (2005 [45])	3†/16 (18.8)
Mjahed et al. (2006 [9])	2/10 (20.0)
Lau et al. (2010 [12])	4/18 (22.2)
Dekker et al. (2011 [3])	4/18 (22.2)
Burroughs et al. (1982 [74])	3/12 (25.0)
Minakami et al. (1982 [32])	4/14 (28.6)

*, including 32, 7, and 7 women with AFLP, HELLP syndrome, and severe pregnancy-related liver disease, respectively; †, including one patient with triplet pregnancy.

Fig. 1

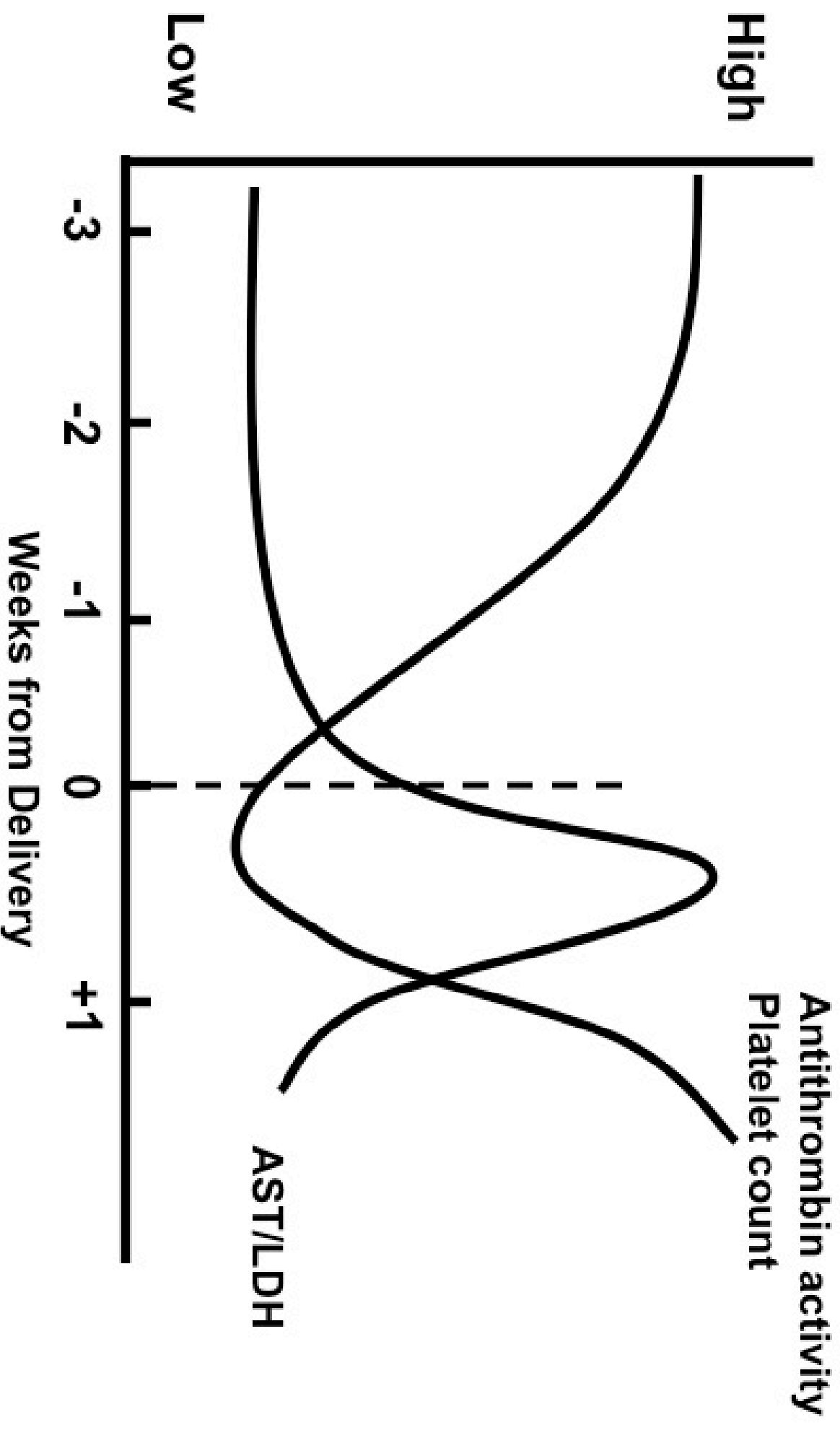


Fig. 2

