Physiological changes of pregnancy and the Swansea criteria in diagnosing acute fatty liver of pregnancy

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journals.sagepub.com/home/obm **Adam Morton and Josephine Laurie**

Abstract

The Swansea criteria are used to assess the likelihood of acute fatty liver of pregnancy. There are significant physiological changes in normal pregnancy in several of the pathology parameters used in the Swansea criteria. This may impact the sensitivity and specificity of the Swansea criteria. Five of the 11 case series reporting laboratory values in acute fatty liver of pregnancy used values divergent from the Swansea criteria. When using the Swansea criteria for diagnosis of acute fatty liver of pregnancy, using pregnancy-specific and/or laboratory-specific reference intervals is recommended. Simpler diagnostic criteria using parameters of hepatocellular damage and hepatic synthetic dysfunction may be an alternative to the Swansea criteria, and further studies investigating the sensitivity and specificity of these parameters would be useful.

Keywords

Acute fatty liver of pregnancy, Swansea criteria, physiological changes, antithrombin III

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Background

Acute fatty liver of pregnancy (AFLP) is a rare disorder of mitochondria β -oxidation causing hepatic microvesicular steatosis. AFLP is estimated to complicate 5–30 per 100,000 pregnancies. AFLP shares clinical and histological features with other mitochondrial hepatopathies including Reye's syndrome, sodium valproate hepatotoxicity and Jamaican vomiting sickness. AFLP also shares clinical and biochemical features with other disorders in pregnancy including severe preeclampsia with haemolysis, elevated liver enzymes and low platelets (HELLP), haemolytic uraemic syndrome/thrombotic thrombocytopenia purpura (HUS/TTP), catastrophic antiphospholipid syndrome, viral and autoimmune hepatitis, bacterial sepsis, leptospirosis and other non-pregnancy-specific causes of fulminant hepatic failure. A 15-month prospective study of liver dysfunction in an obstetric unit in Wales found that 142 of the 4377 pregnant women (3%) had abnormal liver function tests.¹ More than half of the cases of liver dysfunction in pregnancy in the study were due to preeclampsia (PET) and HELLP syndrome. Five women had AFLP, a much higher incidence than had been previously reported. The Swansea criteria were proposed to enable the diagnosis of AFLP while avoiding liver biopsy in patients who are frequently

coagulopathic and thrombocytopenic.¹ The criteria consist of 14 clinical, pathologic and radiologic features. Presence of six or more features in the absence of another explanation is consistent with the diagnosis of AFLP. The symptoms and radiological features in the Swansea criteria vary with regard to their sensitivity and specificity for AFLP. Abdominal pain is a common feature of both HELLP syndrome and AFLP. Transient diabetes insipidus is relatively specific for AFLP though not commonly seen in the condition. Ascites may occur in severe PET as well as AFLP, and bright liver on ultrasound has been reported in only 25% of patients. The authors of the Swansea criteria based normal values for pathology tests on reference intervals for the non-pregnant state. Several case series of women with presumed AFLP have evaluated the performance of the Swansea criteria. Only one case series has assessed the Swansea criteria against biopsy-proven hepatic microvesicular steatosis, finding

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a sensitivity and specificity of 100% and 57%, with positive and negative predictive value of 85% and 100%, respectively.²

Physiological changes result in alterations in reference intervals for many laboratory values in pregnancy. These changes, together with variations related to the assay used, and the population assessed, may impact the sensitivity and specificity of laboratory values used in the Swansea criteria in diagnosing AFLP.

Purpose

To review the changes in reference intervals during pregnancy for blood parameters used in the Swansea criteria and to review other measures of hepatic synthetic function that may be useful in the diagnosis of AFLP.

Methods

A Medline search was performed to investigate how pregnancy physiology impacts those laboratory values that are used in Swansea criteria. Previous case series of AFLP were reviewed for prevalence of abnormalities in laboratory measures of the Swansea criteria and variations in reference intervals for these laboratories.

Results

Physiologic changes in laboratory parameters of Swansea criteria during pregnancy

Reference intervals may vary significantly between laboratories as a result of different assays and testing

methods, and diverse populations being sampled. Wherever possible clinicians should rely on trimester-specific reference intervals determined by the laboratory where a test is performed. AFLP is a disorder of the third trimester or peripartum period. Many of the laboratory investigations utilised in the Swansea criteria have significant changes during pregnancy compared with non-pregnant values (Table 1).

Measures of hepatic function

Prothrombin time (PT) is reduced by 10%–15% in third trimester compared with non-pregnant adults.^{3–8} Authors have quoted reference intervals of 8.5–11.05, 8.5–12.4 and 9.5–12.6 s for third trimester.⁹

Pregnancy is associated with a mild fall in serum albumin.^{10,11}

The level of glucose that is diagnostic of hypoglycaemia in the non-diabetic non-pregnant individual is not well defined. The value of less than 4 mmol/L for hypoglycaemia has been adapted from the level at which individuals with diabetes mellitus commonly develop adrenergic hypoglycaemic symptoms. Hypoglycaemia during 72-h fasting tests in individuals without diabetes mellitus has variously been defined as plasma glucose of less than 2.3–2.7 mmol/L depending on the institution.^{12–15} Fasting glucose levels fall by 0.2 mmol/L in first trimester of pregnancy compared with preconception values, with a further slight fall in third trimester.¹⁶

While not a feature in the Swansea criteria, low serum cholesterol may be useful in the diagnosis of AFLP. Serum cholesterol rises from second trimester due to increased hepatic production.¹⁷ Several studies

Table 1. Comparison of Swansea criteria values with non-pregnant and third trimester reference intervals (includes additional measures of hepatic synthetic function).

Test	Non-pregnant	Swansea criteria	Third trimester	Pregnancy change
Se bilirubin ($\mu\text{mol/L}$)	5–20	>14	2–20	Nil
Hypoglycaemia (mmol/L)	? < 2.3	<4	?	?
AST (u/L)	12–38	>42	4–32	↓
ALT (u/L)	7–41	>42	2–25	↓
PT (s)	9.4–16.5	>14	8.5–11.1	↓
APTT (s)	27–37	>34	25.6–42.5	Nil
Mean ammonia ($\mu\text{mol/L}$)	31 $\pm$ 3.2	>47	27.3 $\pm$ 1.6	Nil
White blood cells (cells/ μL)	4–11,000	>11,000	6–17,000	↑
Se Cr ($\mu\text{mol/L}$)	50–90	>150	30–90	↓
Se urate (mmol/L)	0.15–0.34	>0.34	0.19–0.38	Nil
Fibrinogen (g/L)	2.33–4.96	–	3.73–6.19	↑
Antithrombin III (%)	70–130	–	82–116	Nil
Cholesterol (mmol/L)	2.8–5.2	–	5.9–7.2	↓

Note: Reference intervals will vary depending on the population tested and the assay used. Wherever possible, values for reference intervals should be individualised to the laboratory where the test is performed. ALT: alanine aminotransferase; AST: aspartate aminotransferase; Cr: creatinine; PT: prothrombin time; Se: serum; ?: uncertain value.

have described hypocholesterolaemia in AFLP with overall mean serum total cholesterol of 2.7 mmol/L, values ranging between 0.7 and 4.2 mmol/L.^{18–22} One study reported mean cholesterol levels of 5.4 mmol/L in HELLP syndrome and 1.9 mmol/L in women with AFLP, suggesting low cholesterol may be useful in distinguishing between the two disorders.¹⁹

Serum ammonia (NH₄) levels fall significantly during pregnancy.¹¹

Markers of hepatocellular damage

Pregnancy is associated with mild falls in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin (bili).^{10,23}

Other Swansea criteria parameters

Serum creatinine (Cr), urate and urea fall by approximately 25% early in first trimester due to a 50%–60% rise in renal plasma flow and glomerular filtration rate.^{11,23,24} Towards the end of third trimester, renal plasma flow declines to preconception rates and Cr trends back towards pre-conception values.

White blood cell (WBC) count increases significantly in uncomplicated pregnancy due to neutrophilia.^{25–27} Mean WBC counts of 10,000–16,000 cells/ μ L with an upper level of 29,000 cells/ μ L have been reported during delivery. Leucocytosis is not a discriminating feature in pregnant women with hepatic injury being common to AFLP, severe PET/HELLP, sepsis and HUS/TTP. Leucocytosis may also be induced by glucocorticoid administration to assist fetal lung maturity.

Measures of coagulopathy

Antithrombin III (ATIII) level has been considered to be helpful in the diagnosis of AFLP. ATIII may be low due to reduced hepatic synthesis, altered transcapillary flux ratio, consumptive coagulopathy and urine loss with proteinuria.^{28,29} An ATIII level of less than 65% may be useful in the diagnosis of AFLP.^{19,30} Review of 61 cases in the literature of women diagnosed with AFLP found a mean ATIII level of 16.1% (range 0–69%). Studies examining possible physiologic changes in ATIII during uncomplicated pregnancy have revealed inconsistent results. Several studies described no change in ATIII throughout pregnancy compared with values prior to conception.^{5,31–34} Other authors reported a fall in ATIII from mid-trimester, third trimester values being 13%–20% lower than non-pregnant values.^{9,35,36} Reductions in ATIII during pregnancy were greater in twin than in singleton pregnancies.³⁶ Immediately after delivery, ATIII levels fall reaching a nadir (mean ATIII 76%)

at 12-h postpartum, before returning to baseline 72-h postpartum.³⁵

ATIII activity is lower in preeclampsia than in uncomplicated pregnancy, with mean levels ranging between 60% and 85% in five studies.^{37–42} Similarly mean levels of ATIII ranged between 62% and 80% in HELLP syndrome.^{19,38,40,41} Low ATIII is thought to occur as a result of increased consumption rather than increased urine losses.⁴³

Several case series have also examined the prevalence of disseminated intravascular coagulation (DIC) in AFLP. Fibrinogen levels rise significantly during pregnancy, and the use of non-pregnant reference intervals may underestimate the prevalence of DIC.^{44,45} A fibrinogen level less than 3g/L together with platelet count less than 50 and prolonged PT and APTT is consistent with DIC in pregnancy. A pregnancy modified score taking into account the physiological changes in PT, fibrinogen and platelets reported a sensitivity of 88% and specificity of 96% for the diagnosis of DIC.⁴⁶

Coagulopathy/DIC is far less prevalent with HELLP syndrome than in AFLP. Six studies described DIC complicating 5.6%–13% of cases of HELLP syndrome.^{19,47–51} A 20-year review found that DIC complicated only 0.2% of cases of severe PET.⁵²

In summary, the values in the Swansea criteria for hypoglycaemia and elevated white cell count may result in reduced specificity for diagnosing AFLP, as many patients meeting these criteria will be in the normal reference interval for third trimester. Similarly, the values for PT, NH₄ and Cr could result in reduced sensitivity as women with abnormal renal and hepatic synthetic function for third trimester may be excluded.

Previous case series of AFLP

Table 2 summarises the prevalence of abnormal laboratory findings in case series of more than five patients diagnosed with AFLP as well as previously unpublished data from our institution. The proportion of women with abnormal values was not possible in some series where only the mean or range of results was reported. Five of the 11 published studies had deviations from the laboratory values defined in the Swansea criteria. These deviations are summarised below the table. Similarly, the cut-off levels for fibrinogen used in defining DIC varied from less than 2.5 g/L to less than 1 g/L.

Elevated values for bilirubin, AST/ALT and WBC count were seen in almost all patients. The proportion of individuals with elevated Se creatinine and hypoglycaemia varied significantly between case series. Coagulopathy is a near-universal feature of AFLP. The case series in Table 2 reporting significantly

Table 2. Rate of positive results for individual Swansea criteria in case series of acute fatty liver of pregnancy.

Author	n	Bili (%)	Glu (%)	Urate (%)	WBC (%)	AST/ALT (%)	NH ₄ (%)	Cr (%)	PT/APTT (%)	DIC (%)
Knight et al. ⁵³	57	100	78	88	98	100	50	58	87	–
Lau et al. ⁴³	18	100	61	–	–	100	–	83	100	61
Vigil-De Gracia et al. ²⁷	35	–	94	–	91 ^a	–	–	94	–	77
Mellouli et al. ⁵⁴	19	79 ^a	53 ^a	100 ^a	–	100	–	63 ^a	–	58
Dwivedi et al. ⁵⁵	7	100	57	100	–	100	–	100	100	57
Nelson et al. ⁴⁶	51	100	18 ^a	–	98 ^a	100	–	96 ^a	48 ^a	48
Zhou et al. ⁵⁶	28	100	75	–	–	100	–	82	100	21
Cheng et al. ⁴⁵	32	100	–	–	–	100	–	81	100	16
Xiong et al. ⁵⁷	25	100	– ^a	–	92	96	–	72	100 ^a	20
Zhang et al. ⁴⁴	56	88	57 ^a	–	– ^a	88	–	52 ^a	54 ^a	32
Wang et al. ⁵⁸	52	90	42	9.6	81	85	–	71	87	–
Axe et al. ⁵⁹	20	85	40	95	85	100	20	65	55	–
Mater ^b	17	100	47	–	94	100	46	100	100	–

Note: Vigil-DeGracia et al.: WBC > 13,000 cells/ μ L; Mellouli et al.: Cr > 120 μ mol/L; urate > 0.36 mmol/L; glu < 2.8 mmol/L; bili > 20 μ mol/L; Nelson et al.: bili > 19 μ mol/L; glu < 3.3 mmol/L; PT > 15s; WBC > 13,000 cells/ μ L; Cr > 88 μ mol/L; Xiong et al.: bili > 17 μ mol/L; glu < 2.8 mmol/L + symptoms hypoglycaemia; International normalised ratio > 1.5; Zhang et al.: glu < 3.5 mmol/L; WBC > 10,000 cells/ μ L; Cr > 102 μ mol/L; PT > 14.5s. ALT: alanine aminotransferase; AST: aspartate aminotransferase; bili: bilirubin; Cr: creatinine; DIC: disseminated intravascular coagulation; Glu: glucose; NH₄: ammonia; PT: prothrombin time; Se: serum; WBC: white blood cell.

^aDeviations from Swansea criteria (summarised in the above 'Note').

^bPreviously unpublished data.

lower rates of coagulopathy are likely to have been due to PT criteria of >14.5 and >15 s, respectively.^{20,22}

Conclusion

The diagnosis of AFLP has immediate implications regarding delivery of the baby, as well as considerations regarding genetic mutations and the health of the child, and the risk of recurrence in subsequent pregnancy. As a hepatic microvesicular disorder, one might expect the cardinal features of AFLP to be those of hepatocellular damage and impaired hepatic function. Elevated hepatic transaminases, hyperbilirubinaemia and coagulopathy appear to be near-universal in patients with AFLP, and absence of any of these features should prompt consideration of an alternative diagnosis. Encephalopathy, elevated ammonia levels, hypoglycaemia and transient diabetes insipidus are relatively specific for hepatic injury and strongly support the diagnosis of AFLP but may be present in only a minority of patients with the condition. The remaining features of the Swansea criteria are less specific in differentiating AFLP from other disorders.

The near-universal presence of coagulopathy together with low ATIII levels in AFLP appears valuable in distinguishing AFLP from HELLP syndrome in most cases. Further studies comparing cholesterol levels in AFLP and HELLP would be worthwhile. The combination of hyperbilirubinaemia, elevated hepatic aminotransferases, coagulopathy and ATIII level of less than 65% in the absence of an alternate cause of acute

hepatic failure could be considered as an alternative to the Swansea criteria. Studies assessing the sensitivity and specificity of this approach in diagnosing AFLP would be valuable. Where the Swansea criteria are used, consideration should be given to the use of reference intervals specific to the gestation of pregnancy at the testing laboratory. Where diagnostic values are equivocal, prompt delivery should be considered given the significant maternal and fetal morbidity and mortality with AFLP.

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Contributorship

AM and JL reviewed the literature, compiled the data on the Mater series and wrote the manuscript.

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