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Review

Liver Diseases Specific to Pregnancy

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SUMMARY

During pregnancy, there are some changes in the liver that occur physiologically, such as alternations in blood flow and hepatic cholesterol synthesis and secretion. However, liver diseases specific to pregnancy can occur, and the differential diagnosis from diseases coincidental with pregnancy or pre-existing liver disease is mandatory for proper therapeutic algorithms. Hyperemesis gravidarum develops in 1-20/1000 pregnancies. Intrahepatic cholestasis of pregnancy is the second most common cause of jaundice in pregnancy, mutations in the MDR3 biliary canalicular protein have been found, and ursodeoxycholic acid is considered the most effective therapeutic option. Acute fatty liver of pregnancy (AFLP) occurs in about 1 /14000 pregnancies and in some cases is associated with homozygous long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency in the fetus with a heterozygote mother. AFLP has a wide range of severity and a large degree of overlap in clinical and laboratory findings with HELLP (haemolysis, hepatic enzyme elevation, and low platelets) syndrome and pre-eclampsia/eclampsia. The latter is the major cause of maternal death in developed countries associated with complications, such as hepatic rupture and early delivery is considered the key component for reducing mortality.

Key words: pregnancy, liver disease, hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, acute fatty liver, eclampsia, HELLP

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INTRODUCTION

All major organ systems undergo physiological changes during pregnancy, and the results of clinical examinations and laboratory investigations should be interpreted accordingly. The liver exhibits a range of altered functions, including changes in blood flow and hepatic cholesterol synthesis and secretion. Gallbladder motility decreases while the lithogenic index of bile increases.[1] Hematocrit, serum urea, uric acid, albumin, and total protein values decrease, and the presence of placental and bone isoenzymes generates an increase in alkaline phosphatase.[2] Cholesterol and triglyceride levels increase, while aminotransferase concentrations remain unchanged. Total and free bilirubin concentrations are lower in all trimesters, while conjugated bilirubin and γ-glutamyltransferase (γ-GT) levels are reduced only in the second and third trimesters.[3] The incidence of jaundice – the most common clinical manifestation of liver disease – is low, occurring in approximately one in 1500 pregnancies.[4] Although *post partum* abnormalities in liver function can occur in hepatically uneventful pregnancies, normal functionality is resumed within 5–10 days.[5]

In the clinical setting, it is useful to classify liver diseases in pregnancy into one of three categories:

- Those specific to pregnancy.
- Those coincidental with pregnancy
- Those that are already established

This article will focus on the epidemiology, pathogenesis, clinical and histological features, management, and outcome of liver diseases specific to pregnancy, which fall into 4 different categories: hyperemesis gravidarum, intrahepatic cholestasis of pregnancy (ICP), acute fatty liver of pregnancy (AFLP) and hypertension-associated liver dysfunction. The latter includes pre-eclampsia/eclampsia, liver rupture/infracts and hemolysis, abnormal liver function tests and low platelet levels (HELLP) syndrome.

Recent advances in the understanding of pathogenesis of these diseases [e.g. the association of AFLP and ICP with long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency and mutations in the MDR3 biliary canalicular protein, respectively] give the opportunity for prompt diagnosis and genetic testing in the future, while new therapeutic interventions (e.g. ursodeoxycholic acid in high dose for ICP) have improved maternal and fetal outcome[6]. Although more research and clinical trials are required, it is important to raise the awareness of these conditions among clinicians because they are frequently associated with adverse maternal and fetal outcome. The main clinical features of, and treatment strategies for, these conditions are summarized in Tables 1 and 2, respectively.

HYPEREMESIS GRAVIDARUM

In the first trimester of a normal pregnancy, nausea and vomiting frequently occur[7] and are associated with faster-than-usual gastric dysrhythmias.[8] If atypically prolonged, these symptoms may lead to intense weight loss, dehydration, and mild jaundice, resulting in a condition known as hyperemesis gravidarum; this occurs in between 1–20 in 1000 pregnancies.[9] Transient hyperthyroidism may occur in 60% of such gestations owing to the thyroid-stimulating activity of human chorionic gonadotropin.[9] In addition, aminotransferase levels may be raised, usually by up to 250 IU/L[9].

Hyperemesis gravidarum is associated with age <20 years, nulliparity, obesity, preexisting diabetes and non-

Table 1. Clinical features of the most common liver conditions that occur in pregnancy.

Condition	Main symptoms	Trimester	Bilirubin	Transaminases	Platelets	Other features	Maternal mortality	Fetal mortality	Recurrence of liver disease in subsequent pregnancies
Hyperemesis gravidarum	Prolonged nausea and vomiting	1st	↑	↑ Up to <250 IU/L)	Normal levels	Ketonuria	rare	rare	10%-16%
Intrahepatic cholestasis of pregnancy	Pruritus	2nd–3rd	↑↑↑	↑ Up to <250 IU/L)	Normal levels	Bilirubinuria	rare	0.4%-1.4%	45%-70%
Acute fatty liver of pregnancy	Epigastric/ right upper quadrant pain*, malaise, vomiting	3rd	↑	↑↑ Up to <500 IU/L)	↓	High uric acid levels, proteinuria, hypertension, peripheral edema	7%-18%	9%-66%	20%-70% if there is long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) defect
Pre-eclampsia	Epigastric/ right upper quadrant pain*, malaise, vomiting	2nd–3rd	Normal levels	↑	Normal levels or ↓	High uric acid levels, proteinuria, hypertension, peripheral edema	0.4%-6.1%	0.5%-0.9%	5%-7% in mild pre-eclampsia; 20%-65% in severe pre-eclampsia
HELLP syndrome	Epigastric/ right upper quadrant pain*, malaise, vomiting	2nd–3rd (and *post partum*)	↑	↑	↓↓	Hypertension and proteinuria (but sometimes both absent)	1%-25%	7%-20%	2%-19%

** Sudden, severe pain may indicate hepatic hematoma and/or rupture.*
HELLP: hemolysis, elevated liver enzymes, low platelet count.

Table 2. Current treatment strategies for liver diseases specific to pregnancy

Liver disease	Treatment strategies
Hyperemesis gravidarum	Rehydration, nutritional support, anti-emetics
Intrahepatic cholestasis of pregnancy	Early delivery, close fetal monitoring
	First-line treatment with UDCA. Less-effective alternatives include dexamethaxone (to aid fetal lung maturation), *S*-adenosyl-L-methionine, and cholestyramine
	Vitamin K and other fat-soluble vitamins, particularly in patients receiving cholestyramine
Acute fatty liver of pregnancy	Immediate delivery, supportive measurements during and after delivery similar to those used for fulminant liver failure
Hypertension-associated liver dysfunction	
Pre-eclampsia and eclampsia	Immediate delivery, control of hypertension, management of complications such as liver hematoma and seizures
HELLP syndrome	Immediate delivery, management of complications such as liver hematoma, multi-organ dysfunction, disseminated intravascular coagulation, renal failure, abruptio placentae, plasma expansion, plasmapheresis, prostacyclin, steroids
Liver infarcts, hematomas, and rupture	Conservative management, laparotomy, liver transplantation (very rare).
Budd Chiari syndrome	Anti-coagulation, radiological or surgical shunting, liver transplantation (rare)

HELLP: hemolysis, elevated liver enzymes, low platelet count; UDCA: ursodeoxycholic acid.

smoking status[10;11]. It is rare for a sufferer to experience a recurrence of the condition in subsequent pregnancies[9]. In those affected by hyperemesis gravidarum, the balance of liver enzymes will return to normal when dehydration and malnutrition are corrected. With regard to treatment, both steroids[12] and ondansetron[9] are effective.

Rare complications of hyperemesis gravidarum include esophageal rupture, Wernicke's encephalopathy, central pontine myelinolysis, retinal hemorrhage, and spontaneous pneumomediastinum.[9]

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

After acute viral hepatitis, intrahepatic cholestasis of pregnancy (ICP) is the second most common cause of jaundice in pregnancy, occurring in 0.5–1% of pregnancies in the second or third trimester.[3;13] In terms of pathogenesis, mutations exist in different exons of the gene encoding the MDR3 biliary canalicular protein, and such mutations may lead to raised levels of γ-GT.[14;15] At least 10 different *MDR3* mutations associated with ICP have been identified[6], and are present in 30% of ICP cases in the UK.[16] One report has shown that certain *MDR3* gene variants (*ABCB4*) are associated with a severe form of ICP.[17] Another study demonstrated that splicing mutations in the *MDR3* gene result in ICP (although γ-GT levels were normal), and may be associated with stillbirths and gallstone disease.[18] *MDR3* mutations are also found in progressive familial intrahepatic cholestasis.[19]

The initial symptom of ICP is pruritus, and in mild cases there is no jaundice (pruritus gravidarum). In the presence of other skin lesions, alternative causes of itching may initially be considered. Jaundice usually follows pruritus after approximately 2 weeks, with dark urine and pale stools. Right upper quadrant pain and tender hepatomegaly are unusual. ICP lasts for the duration of pregnancy and resolves within 2–4 weeks of delivery, with no sequelae. In ICP, serum bilirubin levels do not generally exceed 5.8 mg/dL[12] Bile acid levels become raised, while aminotransferase levels rarely surpass 250 IU/L[19]. As stated earlier, γ-GT measurements may be normal [12].

Histologically, there is centrilobular cholestasis without necrosis or inflammation in ICP. However, liver biopsy is not required for diagnosis – this is based on the clinical and biochemical findings after exclusion of other liver diseases. Serum levels of glutathione S-transferase may discriminate between ICP and pruritus gravidarum,[20] but this area requires further study.

Treatment with dexamethasone 12 mg/day for 1 week (then tapered over the subsequent 3 days) may improve pruritus by suppressing fetoplacental estrogen synthesis.[21] Although dexamethasone aids fetal lung maturation,[21] its effectiveness in ICP remains debatable. Indeed, it is less effective than ursodeoxycholic acid (UDCA),[22] which, when administered at ≥1 g/day (up to 2 g/day), is safe, modifies the bile acid pool (possibly via post-transcriptional mechanisms), relieves pruritus, and improves liver function within 2 weeks.[6;23;24] Studies have demonstrated

that UDCA is also more effective than *S*-adenosyl-L-methionine and cholestyramine[25;26], and it is presently the first-line treatment for ICP. Some authorities recommend routine delivery of the baby before 38 weeks' gestation in ICP, while others only endorse induction if fetal distress occurs, or if jaundice is present at 36 weeks.[27]

Vitamin K deficiency due to cholestasis may increase prothrombin time and raise the risk of fetal and *post partum* hemorrhage. Therefore, vitamin K should be administered parenterally at least 6 h before delivery, particularly in patients who are receiving cholestyramine; this is because the latter therapy may worsen steatorrhea, which exacerbates vitamin K deficiency and may subsequently lead to hemorrhage.[28]

In terms of outcome and complications, ICP is associated with an increase in miscarriage, premature labor, and perinatal mortality, but there is no direct relationship between nutritional state and fetal prognosis.[12] Recurrence of pruritus can occur with subsequent pregnancies, and may also occur in menstrual disturbances associated with excess estrogen, or use of the oral contraceptive pill (50% of women with cholestasis related to oral contraceptives have a history of ICP).[29]

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) affects approximately one in 14000 pregnancies,[30] and male births are more common among women with this condition.[31;32] AFLP occurs in the last trimester, usually between weeks 34 and 36 of gestation; earlier presentation is so exceptional that alternative diagnoses should be sought in such cases.

Several cases of AFLP are associated with homozygous long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency in a fetus who has a heterozygote mother for LCHAD deficiency, whereby the latter cannot metabolize the extra free fatty acids that are not metabolized by the fetus.[33;34] However, several factors appear to contribute to this fetal-maternal interaction.[35] LCHAD deficiency is caused by a genetic defect of mitochondrial trifunctional protein.[36] Careful observation of children born to mothers with AFLP is warranted as they may be homozygous for LCHAD deficiency. These children are at risk of hypoglycemia, fatty liver, dilated cardiomyopathy, progressive neuromyopathy, and sudden infant death syndrome;[37;38] thus, early diagnosis and dietary intervention could be lifesaving.[39] Fortunately, prenatal diagnosis is possible.[40] AFLP is also associated with HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome[41], which will be discussed in greater detail below. The G1528C mutation resulting in the conversion of glutamic acid to glutamine (E474Q), has been found to be present in 20% of AFLP cases.[42] Interestingly, short chain acyl-CoA dehydrogenase deficiency has also been associated with AFLP.[43]

Burroughs et al,.[3], and others, have reported that women with AFLP have an increased frequency of pre-eclampsia signs (approximately 50%), are more likely to be in primigravidae (50%), and have a 10–15% increase in the incidence of twin pregnancies.[31] These features are also present in cases of toxemia during pregnancy. Indeed, there is a large degree of overlap between liver diseases and toxemia, leading to a disease spectrum known as "hepatic toxemia", which incorporates HELLP syndrome.[44]

In AFLP, abdominal tenderness is common and ascites may be present. Non-specific symptoms, such as nausea, vomiting and flu-like illness in the last trimester of gestation may be suggestive of AFLP and should be explored accordingly.[45] Altered states of consciousness, including coma and flapping hand motions, may be present. The peripheral edema, hypertension, and proteinuria that are present in approximately 50% of AFLP cases may lead to an initial diagnosis of pre-eclampsia.[31] Occasionally, AFLP is diagnosed "late" as a cause of *post partum* jaundice.[46]

Neutrophilia (usually $\geq 15\times10^9$/L) and thrombocytopenia (typically $<100\times10^9$/L) are almost universally noted in cases of AFLP. Serum aminotransferase levels rarely rise above 500 IU/L,[32] and fall immediately following delivery. Bilirubin concentration levels may be markedly increased and usually peak *post partum* (although jaundice may be absent in up to 10% of cases of AFLP). Gammaglobulin concentrations and quantitative immunolobulins are not elevated, or only minimally so,[31] and this can help to distinguish AFLP from acute viral hepatitis. Alkaline phosphatase concentrations are raised. Prothrombin and partial thromboplastin times may be increased[31] and disseminated intravascular coagulation can also be present.[47] Plasma urea, uric acid, and creatinine levels are usually elevated, even when jaundice is absent, and these continue to rise until delivery. Urinary sodium excretion levels are low,[31] while hypoglycemia, hyponatremia and hyperkalemia may be present. Uric acid concentration levels may increase days before symptoms of AFLP become manifest;[48] therefore, they serve as a pointer towards early diagnosis.[31]

As AFLP occurs solely in the last trimester, the differential diagnoses lie between acute viral or drug-induced hepatitis and toxemia of pregnancy (including HELLP

syndrome).[49] However, obstetric causes of renal failure should also be considered in differential diagnosis, for example hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).[50]

Immediate delivery is the key to managing both AFLP and toxemia. If the AFLP symptoms are mild, careful fetal monitoring can be used to try to prolong gestation;[44] however, the progression of the maternal illness may be unpredictable. Vaginal delivery should be attempted first, while prophylactic antibiotics are recommended to prevent uterine infections.[51] A cesarean section may be performed using spinal anesthesia if coagulation is close to normal; otherwise, general anesthesia is preferable to avoid bleeding caused by spinal puncture. The treatment regimen for the mother is the same as that which would be adopted for any patient with fulminant liver failure.

There is currently a wide clinical spectrum of AFLP severity that includes a substantial proportion of less-severe cases, It is estimated that the overall maternal and fetal mortality rates are 7–18% and 9–23%, respectively,[6] but more recent studies have shown that maternal and neonatal outcomes are better than previously reported, possibly related to improved ascertainment.[52] Severe AFLP can result in the same complications as those seen in fulminant liver failure, namely subcapsular hematoma, rupture of the liver[53], and fat emboli.[54]

HYPERTENSION-ASSOCIATED LIVER DYSFUNCTION OF PREGNANCY

Hypertensive pregnancy disorders incorporate a wide range of clinical conditions, including chronic and gestational hypertension, pre-eclampsia, eclampsia, and HELLP syndrome. Such conditions are considered to be major causes of maternal, fetal, and neonatal morbidity, and may be life-threatening for both mother and fetus. Indeed, in developed countries, hypertension and pregnancy-induced hypertension are the principal causes of maternal death.[55]

Pre-eclampsia and eclampsia

Pre-eclampsia comprises hypertension, edema, and proteinuria. The condition arises in the third trimester and occurs in 5–10% of pregnancies. Pre-eclampsia is diagnosed where one of the following scenarios occurs. Firstly, where there is rapid weight gain indicative of edema (often manifesting as ankle edema) together with proteinuria and hypertension in the second or third trimester. Secondly, if the mother has a blood pressure measurement of >140/90 mmHg in the absence of previous hypertension. Thirdly, if there is an increase of either 30 mmHg systolic BP or 15 mmHg diastolic BP in cases involving pre-existing hypertension.[55] A diagnosis of eclampsia, by definition, requires the occurrence of fits. Several other symptoms and conditions may occur in between the states of mild pre-eclampsia and eclampsia, including the following:

- Symptomatic end-organ disease involving the brain, kidneys, and liver.
- Headache.
- Visual disturbances.
- Upper abdominal pain, which may mimic "surgical abdomen" [55].
- Oliguria with renal failure.
- Tender but not enlarged liver.

With mild hypertension, 24% of patients have abnormal aminotransferase levels (as demonstrated by a study involving a large consecutive series of pregnant women who were registered antenatally,[55] increasing to >80% in those with severe hypertension. Bilirubin levels do not increase unless there is hemolysis or hepatic infarction, while antithrombin III levels are inversely correlated with outcome in severe pre-eclampsia.[56]

For such hepatic abnormalities, the management is the same as for pre-eclampsia. Early delivery is the key to improving both the hypertensive and liver complications. The results of liver function tests follow a standard pattern after delivery: aminotransferase levels decrease after 24 h and bilirubin levels fall within 72 h, but measures of alkaline phosphatase and γ-GT rise on day 5 or 6, peak on day 10, and return to normal within 8 weeks[57]. A computed tomography (CT) or ultrasound scan should be performed to identify subclinical liver hematoma and infarcts[58] caused by segmental vasospasm,[59] or microangiopathy.

Cerebral hemorrhage is the major cause of mortality in patients with eclampsia, but hepatic complications may account for up to 16% of deaths, which are usually caused by hepatic rupture.[59] Periportal hemorrhage occurs in increasingly serious cases of eclampsia, and in the most severely affected patients these hemorrhages develop into large infarcts and hematomas that may rupture[60;61]. Liver infarcts may also be secondary to hepatic arterial thrombosis, which is associated with very high aminotransferase levels; these may resolve spontaneously.

Liver rupture

Hepatic infarcts, hematomas, and liver rupture in pregnancy are associated with severe pre-eclampsia or eclampsia in 80% of cases[62] and, to a lesser degree, with HELLP

syndrome and AFLP[53]. Liver rupture presents as sudden abdominal pain associated with nausea and vomiting, and shock may develop very quickly.[62] The initial treatment of choice is the conservative management of hepatic hematomas; however, facilities for urgent laparotomy should be available. Liver transplantation may be necessary and has been shown to be successful,[63] but has only rarely been performed in this setting.

HELLP syndrome

A syndrome of hemolysis, abnormal liver function tests, and low platelet levels was described in 1971,[64] and was given the acronym HELLP in 1982.[65] From a well-categorized series of 1153 patients with pre-eclampsia, 112 (9.7%) with HELLP syndrome were identified over a period of 8 years[66]. Recently, it was found that women heterozygous for factor V Leiden have an increased risk of developing HELLP syndrome[67], while placental CD95 ligand (CD95L) has been shown to act systemically to cause liver damage in patients with HELLP syndrome, and blockade of CD95L reduced liver damage via inhibition of apoptotic mechanisms.[68] This finding may eventually lead to new therapies, although the relationship between HELLP syndrome and defects in fatty acid oxidation requires further evaluation.[69]

The HELLP syndrome is considered a microangiopathic hemolytic anemia associated with vascular endothelial injury leading to platelet consumption.[70] There are no diagnostic clinical features to distinguish HELLP syndrome from pre-eclampsia[71]. HELLP syndrome may present with abdominal pain, nausea vomiting and may be associated with, or precede, hypertension,[72] with or without proteinuria.[73] It may occur early in pregnancy as a complication of antiphospholipid syndrome,[74] although 30% of cases arise *post partum.*[75] The syndrome, which carries an increased risk of liver infarction and hemorrhage,[75] occurs more frequently in older, white, multiparous women who present with late pre-eclampsia.[66]

As with pre-eclampsia, a diagnosis of the HELLP syndrome requires the presence of hypertension, edema, and proteinuria;[39] however, the diagnostic criteria are inconsistently applied.[6] In the aforementioned series, a diagnosis of HELLP syndrome was only made when platelet counts were $<100\times10^9$/L; a blood film showed fragmented red cells; and bilirubin, lactate dehydrogenase, and aspartate aninotransferase levels were elevated (the latter by four standard deviations above the norm).[66] In a different series, the diagnosis of HELLP syndrome was based simply on increased aminotransferase levels, a platelet count of $<150\times10^9$/L, and a serum haptoglobin level of <0.7 g/L.[76]

The treatment for HELLP syndrome is delivery of the fetus; however, spontaneous recovery can occur before delivery.[77] A good outcome is possible with conservative management,[78] or the use of plasma expansion, plasmapheresis, prostacyclin, and steroids administered *pre-* [79] or *post partum.*[80] Although the steroids may benefit fetal lung maturity and improve the maternal platelet count,[6] whether steroid administration confers any benefit remains controversial.[81;82] Again, liver transplantation has been successfully performed, albeit rarely.[83]

Overlap between AFLP and hypertension-associated liver dysfunction of pregnancy

Many patients with AFLP show signs of pre-eclampsia;[84] therefore, the two conditions may form part of the same disease spectrum, or may be associated with the same metabolic defect, namely LCHAD deficiency. Indeed, both older[85] and newer[59] studies have found fatty livers in a significant proportion of patients with eclampsia. One study involving 41 consecutive patients with pre-eclampsia with or without liver dysfunction revealed that all women had a significant amount of microvesicular fat upon oil red O staining.[86]

Although the association between AFLP and HELLP syndrome or pre-eclampsia is suggested by the frequency with which both conditions occur in mothers of infants who have LCHAD deficiency,[41] this apparent connection may in fact be due to misdiagnosis of AFLP as HELLP syndrome[31;87]. Some sources recommend monitoring platelet counts, as these levels decrease just before HELLP syndrome and AFLP become manifest.[88]

HUS and TTP also have similar presentations to AFLP and the HELLP syndrome.[89]

Budd–Chiari syndrome

Budd–Chiari syndrome refers to hepatic venous outflow obstruction secondary to thrombosis of the hepatic veins or suprahepatic inferior vena cava. It arises due to an increased state of hypercoagulability, which can be caused by factor Leiden or a deficiency of anticoagulation factors such an antithrombin III, or proteins S and C.[90] A thrombophilia screen should be performed if the syndrome is suspected. The syndrome occurs more frequently in pregnancy, principally immediately *post partum*, but may occur as late as 2 weeks afterwards[91]. While the fetus is unaffected, the maternal mortality rate is high.[92]

Acute Budd–Chiari syndrome presents as right upper quadrant pain, jaundice, and ascites, which may rapidly develop into a severe obstruction. A diagnosis

can be established using Doppler ultrasonography and an abdominal CT scan.

In terms of treatment, anticoagulation therapy is mandatory in the long term, but emergency radiological or surgical shunting may also be required.[93] In some cases, liver transplantation is necessary.[94]

CONCLUSION

In conclusion, there are changes in the liver that occur physiologically during pregnancy, but liver diseases specific to pregnancy can occur. The differential diagnosis of these conditions from diseases coincidental with pregnancy and pre-existing liver disease is mandatory for proper therapeutic algorithms. In several cases, immediate delivery is lifesaving for both mother and fetus.

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