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journal homepage: www.casereports.comSurgery for pregnancy-associated primary hepatocellular carcinoma: Report of four cases[☆]Ai-jun Li^{a,1}, Wei-ping Zhou^{b,2}, Jun-hua Lu^{c,3}, Long-jiu Cui^{a,4}, Xiao-yu Yang^{a,5}, Lei Yin^{a,6}, Meng-chao Wu^{d,*}^a Department of the 2nd Special Treatment, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, 225, Changhai Road, Shanghai 200438, China^b Department of the 3rd Liver Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, 225, Changhai Road, Shanghai 200438, China^c Department of the 6th Liver Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, 225, Changhai Road, Shanghai 200438, China^d Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, 225, Changhai Road, Shanghai 200438, China

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ABSTRACT

INTRODUCTION: Hepatocellular carcinoma (HCC) occurring in pregnancy is quite rare. The prognosis is usually poor because of a delay in diagnosis. Reported cases of HCC in pregnancy are largely isolated with no large experience. Thus the effect of pregnancy on the prognosis of patients with HCC and the risk factors of developing HCC in pregnancy are not well documented. Our aim was to review our experience with management of four young pregnant women with HCC.

PRESENTATION OF CASE: Laboratory tests were performed before surgery. We analyzed the effects of age, hepatitis B surface antigens status, cirrhosis at presentation, gestational age of fetus, and maternal outcome.

DISCUSSION: Increase in alpha-fetoprotein (AFP) level was somewhat useful for diagnosis. Three patients died in 5 months, 6 months, and 24 months from HCC recurrence, and another patient is alive without disease 12 months postoperatively.

CONCLUSION: Surgery for HCC during pregnancy should be similar to that for non-pregnant women. Complete excision of tumor without termination of pregnancy provides the greatest chance of survival for women with HCC during pregnancy but depends on gestational age of the fetus. Adjuvant treatments are required to improve the long-term results of this type of surgery. The 28-week gestational week is a critical point of fetal maturation which is very important in deciding whether pregnancy should be terminated or not. The pregnancy was terminated in two of our patients when spontaneous rupture of HCC was diagnosed to save the mother's life.

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1. Introduction

Hepatocellular carcinoma (HCC) occurring in pregnancy is rare. Since 1957, less than 50 cases have been reported worldwide.^{1,2} A comprehensive review by Lau et al.⁵ reported five cases and analyzed an additional 23 cases of HCC in pregnancy reported in the literature. Only three mothers underwent liver resection. Live infants were developed in 57% of cases but the maternal outcome was grave. The median survival was shorter than patients who were not pregnant. Choi et al.¹ reported four cases and analyzed an additional 44 cases of HCC in pregnancy. Only 16 mothers got the chance for liver resection. Their overall 6-month and 1, 2, and 3-year survival rates were 50%, 30%, 18%, and 14% respectively. It appears that the morbidity and mortality of HCC during pregnancy has improved over time as the diagnosis tended to be made earlier and patients tended to receive resection and other treatments.⁶ El-Serat et al.⁷



Fig. 1. Magnetic resonance imaging (MRI) showed there was a liver tumor with the size of $10 \times 10 \times 10 \text{ cm}^3$ in the middle liver and a normal male infant of 2.9 kg weight in the uterus below the liver.

reported that HCC were more aggressive with an overall one-year survival of only 23%. Pregnancy with HCC is believed to impart a worse prognosis than in non-pregnant women.^{1,7} Also, in the majority of reported cases, pregnancy was terminated when cancer was diagnosed. Our article describes a single center experience with three patients with pregnancy-associated HCC in the Eastern Hepatobiliary Surgery Hospital between January 2002 and December 2012 and includes the occurrence of rupture and hemorrhage during the puerperal state in two of the four patients.

2. Case reports

Case 1A 27-year-old woman with her first pregnancy presented with HCC with 32-weeks' gestation. She was admitted because of right upper quadrant pain. Laboratory findings included a total bilirubin of 3.5 mol/L, albumin 33.7 g/L, alanine aminotransferase (ALT) 58 iu/L, aspartate aminotransferase (AST) 102 iu/L, and alkaline phosphatase (ALP) 97 iu/L. She was HBsAg (+) anti-HBe (+) anti-HBc (+) HBV-DNA (–). Her alpha-fetoprotein (AFP) was greater than 1000 U/L. Abdominal ultrasonography showed a hypochoic tumor, 10 cm in size in the middle liver. Magnetic resonance imaging (MRI) confirmed a huge lesion in the middle of her liver, $10 \times 10 \times 10 \text{ cm}^3$ (Fig. 1). The plan was to carry out a synchronous middle hepatectomy and C-section.

A normal male infant of 2.9 kg was delivered by Cesarean section. Subsequently, middle lobectomy (segmentectomy of IV, V, and VIII) and cholecystectomy was performed via a subcostal oblique incision. During operation, 30 ml of non-coagulable liquid was present in the abdominal cavity; the liver was not cirrhotic. The patient and baby recovered well after surgery. The pathologic

diagnosis was HCC with clear surgical margins (T1N0M0). One month later, computed tomography (CT) showed multiple tumor recurrences in the liver and the patient died 6 months later. The infant remains well but is positive for the hepatitis B virus surface antigen. Case 2A 24-year-old pregnant woman at the gestational age of 26 weeks was admitted because of right upper quadrant pain. Abdominal ultrasonography revealed a tumor in the left lobe of the liver. Laboratory findings included normal liver function tests but she was positive for hepatitis B surface antigen and her AFP was greater than 1000 U/L. CT showed a 17 cm lesion with an irregular margin in the left liver and some free peritoneal fluid. The diagnosis was made of spontaneous rupture of primary liver cancer, and she underwent Cesarean section where a stillborn fetus weighing 1500 grams was removed. Subsequently a left hepatic lobectomy was performed for a $20 \times 17 \times 16 \text{ cm}^3$ lesion in a non-cirrhotic liver. During operation, 200 ml of a non-coagulable liquid was present in the abdominal cavity. Histopathology showed a HCC with a free resection margin. The patient recovered uneventfully and was discharged home on postoperative day number 8. The patient died in 2 years from HCC recurrence. Case 3A 23-year-old pregnant woman at the gestational age of 16 weeks was admitted because of right upper quadrant pain. Abdominal ultrasonography revealed a tumor in the left lobe of the liver. Laboratory findings included normal liver function tests but she was positive for hepatitis B surface antigen and her AFP was greater than 1000 U/L. CT showed a 7 cm lesion in the left liver. She underwent Cesarean section where a stillborn fetus of 4 months was removed. Subsequently a left hepatic lobectomy was performed for a $6 \times 7 \times 7 \text{ cm}^3$ lesion in a non-cirrhotic liver. Histopathology showed a HCC with a free resection margin. The patient was discharged home on postoperative day number 7. After operation, the patient received two times of transarterial chemoembolization (TACE) from HCC recurrence and died in 5 months after operation. Case 4A 40-year-old female with a two-year history of chronic hepatitis B presented with her first pregnancy at 24 weeks of gestation. Routine abdominal ultrasonography revealed incidentally a tumor mass in the left lobe of the liver. Laboratory values showed positivity for hepatitis B surface antigen and an AFP greater than 1000 U/L. MRI showed a 7 cm space-occupying lesion with a regular margin in the left lobe of the liver. Two weeks before operation, an abortion was performed, and then later a hemihepatectomy was carried out. No cirrhosis was found during the operation. Histopathology showed HCC with a clear resection margin. The patient recovered uneventfully and was discharged home on postoperative day seven. During the following period, the serum alpha-fetoprotein level has remained within the normal range and, at present, the patient remains free of HCC 12 months after hepatectomy.

3. Discussion

The concomitant presence of HCC during pregnancy is rare, but must be considered in populations with a high prevalence of exposure to Hepatitis B virus. The exposure to long-term estrogen and progesterone therapies in women of childbearing age for contraception may further predispose women who are hepatitis B antigen positive to development of HCC. Similarly, a family history of HCC is also pertinent.^{1,10} During pregnancy, the large amounts of human chorionic gonadotropin (HCG), estrogen and placental lactogen secreted from the placenta are believed to promote the growth and reproduction of cancer cells, thus aggravating the aggressiveness of the underlying HCC.^{8–12}

The diagnosis of HCC during pregnancy can also be difficult. Many of the physiologic symptoms of pregnancy can be similar to those of an underlying HCC,^{13–15} such as fatigue, nausea, and vomiting, leading to a delay in diagnosis. Similarly as pregnancy

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