

HEPATOCELLULAR CARCINOMA IN PREGNANCY AND POSTPARTUM PERIOD: A STUDY OF 6 CASES IN NIGERIAN WOMEN.

¹D.A. Ndububa, ²O.N. Makinde, ³O.S. Ojo, ³B.J. Olasode, ⁴V.A. Adetiloye, ⁴O.C. Famurewa, ⁵A.E. Agbakwuru and ²E.O. Orji.

Department of Medicine¹, Obstetrics & Gynaecology² Morbid Anatomy³, Radiology⁴ and Surgery⁵, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria.

ABSTRACT

Six Nigerians women with hepatocellular carcinoma (HCC) in pregnancy and the postpartum period were studied. Their ages ranged from 22 to 37 years with a mean of 28.2 years. Five (83.3%) of the women presented in the postpartum while 1(16.7%) presented during pregnancy. There was co-existing cirrhosis in 5(83.3%) of them. All the 4 women tested for HBsAg were positive. Rapid tumour growth was observed in 2 women who were breastfeeding their babies while on admission. One of the 6 women had a fresh stillbirth at 32 weeks gestation but the other 5 had normal deliveries. Five out of the 6 patients died on admission (after an average of 20 weeks of illness) while 1 patient discharged herself against medical advice. The major causes of death were hepatic failure and intra-peritoneal haemorrhage.

This study shows that the pregnant Nigerian women with HCC may carry her pregnancy to term and have normal delivery. Those women who do not present during pregnancy may do so in the postpartum period. It is suggested that breastfeeding may aid rapid HCC growth and rupture.

KEY WORDS: *Hepatocellular Carcinoma, Pregnancy, Postpartum period, Breastfeeding.*

INTRODUCTION

Hepatocellular carcinoma (HCC) occurs worldwide but it is highly prevalent in countries of South-east Asia and sub-Saharan Africa where hepatitis B virus (HBV) infection and high dietary aflatoxin intake are the main aetiological risk factors^{1,2,3}. The tumour is fairly common in Nigeria with an estimated incidence of 18.4 per 100,000 population per year⁴. HCC is much common in males than females and, like most cancers, it is rare in pregnancy⁵. This raises the possibility that the sex hormones may have a role to play in the development of this tumour. The exact role of the female sex hormones in this regard is not yet clear. While long-term use of oral contraceptives has been associated with benign liver tumours, its association with HCC is still controversial⁶.

A number of cases of HCC in pregnancy have been reported from Nigeria and some other parts of the world but there appears to be no reports of HCC occurring during lactation and the immediate postpartum period. In this paper, we described the clinicopathological features of 6 patients presenting with HCC in pregnancy and postpartum period.

PATIENTS AND METHODS

The six patients described in this study were seen at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Nigeria between 1992 and 1998.

Diagnosis of HCC was made based on the typical clinical features of the tumour together with characteristic real-time ultrasound features (2) and liver histology (4).

Diagnosis of HCC was made during pregnancy in 1 patient and in the postpartum period in 5. Alphafetoprotein (AFP) assay was not done as the test was not available in our hospital. The obstetric history, outcome of management and other relevant findings in the 6 patients are shown in tables 1 and 2.

RESULTS

The ages of the 6 women studied ranged from 22 to 37 years (mean 28.2) and the duration of symptoms before presentation ranged from 3 to 52 weeks (mean 18.85). The duration of hospital admission was from 1 to 24 days (mean 20.4). All the 6 (100%) women had abdominal pain while abdominal distension, early satiety and anaemia were present in 5 (83.3%) of them. Other main clinical findings were jaundice, emaciation, anorexia (4 each, 66.7%), tachycardia, ascites and fever (3 each, 50%). All had hepatomegaly with liver span ranging from 15 to 30 cm (mean 20.4). Hepatic encephalopathy was the most common complication (3 patients, 50%) while haemoperitoneum occurred in 2 patients (33.3%) and intratumour haemorrhage in 1 patient (16.7%). The case by case presentation is given below.

CASE REPORTS

Patient 1

This 30-year old woman, trader, Para 7+0 (5 alive) gave a history of abdominal pain & mass, weight loss, vomiting, poor lactation, early satiety and jaundice of 25 days duration. Her symptoms began in the last trimester of pregnancy, one week before delivery. She had a successful, normal delivery and subsequently presented on the 18th day of the puerperium. Previous pregnancies had been uneventful.

On examination she was emaciated, pale and jaundiced with palmar erythema. The abdomen was asymmetrically distended with visible anterior wall veins. The liver was palpable 14 cm below the costal margin (span = 21 cm) and it was hard, nodular and tender. The HBsAg test was positive and the serum chemistry showed conjugated hyperbilirubinaemia (Total 108 $\mu\text{mol/L}$, conjugated 85 $\mu\text{mol/L}$), elevated liver transaminases (ALT 25 IU/L & AST 198 IU/L; normal ≤ 12) and hypoalbuminaemia (29 g/L; normal = 35-50). Liver USS was supportive of HCC co-existing with cirrhosis. Patient developed hepatic encephalopathy soon after admission and so liver biopsy could not be done. Her condition gradually deteriorated and she died in hepatic failure after 29 days on admission. Autopsy was refused.

Patients 2

This 25-year old woman, tailor, para 1+0 (1 alive), presented at 32nd week gestation with 11 months history of abdominal mass and increasing abdominal swelling. On examination, she was emaciated and had fluffy, scanty axillary & pubic hair, pallor and palmar erythema. She was tachypnoeic with features of right basal pleural effusion. The abdomen was distended and revealed a gravid uterus of 32 weeks fundal height. The liver was palpable 15 cm below the costal margin but 18 cm below the xiphoid (span = 23 cm); it was markedly tender, hard with irregular surface. The HBsAg test was positive and the packed cell volume (PCV) was 27%. Serum chemistry showed normal ALT levels (5 IU/L) and hypoglycaemia (2.3 mmol/L). Abdominal USS demonstrated a single active foetus with cephalic presentation and gestational age of 30.5 weeks. The spleen was enlarged with marked dilatation and increased tortuosity of the splenic vein. The liver USS was consistent with HCC and so an ultrasound diagnosis of normal pregnancy co-existing with HCC and portal hypertension was made. Liver biopsy was done and the histology confirmed HCC.

On the 9th day of admission, patient developed sudden severe hypertension with blood pressure in the range of 170-180/120-130 mmHg. The next day she went into congestive heart failure and the foetal heart was no longer heard. A repeat abdominal USS showed intra-uterine foetal death at 32 weeks gestation. Labour was induced with pitocin drip and this resulted in the delivery of a fresh stillbirth (female baby). On the 15th day of admission (5 days postpartum) she discharged herself against medical advice.

Patient 3

This 37-year old woman, petty trader, Para 7+0 (7 alive), gave a one-year history of right upper quadrant pain (RUQ) and upper abdominal swelling. These symptoms commenced 3 months into her last pregnancy and were associated with anorexia, early satiety and vomiting. She had a normal delivery 6 months before presentation but the RUQ pain grew worse and jaundice developed at the time of delivery. There was positive history of consumption of large quantities of palm wine following each of her 7 deliveries to stimulate breast milk formation and expression.

On examination, she was emaciated, pale, drowsy and jaundiced. The abdomen was grossly distended with moderately severe ascites. The liver was palpable 24 cm below costal margin (span = 30 cm), and was hard, tender and

nodular. She was breastfeeding a 6-month old baby at time of presentation but this was stopped when the liver was observed to be increasing in size. The HBsAg test and serum transaminases were not done but the prothrombin time was deranged. The liver USS showed features of HCC co-existing with cirrhosis. The patient started passing melena stools while on admission. A sharp drop in the PCV occurred in tandem with increasing liver size prompting the suspicion of intra-tumour haemorrhage. Liver biopsy could not be done as a result of this. Patient soon went into shock and deteriorated rapidly despite resuscitative measures. She died after 18 days on admission and autopsy was refused.

Patient 4

This 28-year old woman, trader, had a normal delivery of a live male baby 10 months before presentation. The parity was not stated. Three months prior to presentation (i.e. 7 months post delivery) she developed upper abdominal pain while she was still breastfeeding. Other symptoms were abdominal swelling early satiety, weight loss, fever, anorexia and body weakness.

On examination, she was very ill-looking, emaciated, restless, deeply jaundiced and pale. She had finger clubbing, asterixis and bilateral pitting pedal oedema. The abdomen was grossly distended with scarification marks, visible anterior wall veins and tense ascites. The liver was palpable 10 cm below the costal margin (span = 16 cm), craggy, hard but not tender. Diagnostic paracentesis abdominis yielded free-flowing haemorrhagic ascitic fluid. Apart from the PCV (20%) and the liver USS that showed features of HCC, other investigations could not be done as patient's condition deteriorated very rapidly and she died less than 24 hours after admission. At autopsy there was massive haemoperitoneum and liver necropsy confirmed HCC with concomitant cirrhosis.

Patient 5

This 22-year old woman, petty trader, presented with a 2-month history of body weakness, jaundice, weight loss, fever, diarrhoea, early satiety and abdominal swelling. She had had a normal delivery 7 months before presentation.

On examination, she was ill-looking, emaciated, jaundiced and pale with palmar erythema. The abdomen was grossly distended with umbilical hernia, visible anterior wall veins and severe ascites. The liver was palpable 9 cm below the costal margin (span = 14.5 cm), multinodular, hard and tender. Diagnostic paracentesis abdominis yielded haemorrhagic ascitic fluid. The HBsAg test was positive. The serum chemistry showed conjugated hyperbilirubinaemia (total 101 & conjugated 97 $\mu\text{mol/L}$), ALT 34 IU/L, hypoalbuminaemia (33 g/L) and hypoglycaemia (2.5 mmol/L). The PT was severely deranged. The liver USS showed features consistent with HCC and cirrhosis. Liver biopsy could not be done due to the haemoperitoneum but fine needle aspiration of the liver done earlier was positive for malignant cells. Patient died of respiratory insufficiency (respiratory rate at a point was 76 cycles/min.) resulting from increasing abdominal girth and intra-peritoneal haemorrhage after 18 days on admission.

Patient 6

This 27-year old woman, teacher, para 1+0, was breastfeeding an 8-month old male baby at the time of

presentation. Her symptoms of epigastric pain and mass with frequent stools began 6 months after delivery. She was asymptomatic during pregnancy and her menses had returned one month after delivery but had ceased just before presentation.

The liver was palpable 5 cm below the costal margin but 14.5 cm below the xiphoid, hard, nodular and tender. The HBsAg test was positive. The PCV showed erythrocytosis (55%) and initial derangement of the PT. This was corrected after parenteral vitamin K injections. The serum ALT was elevated (34IU/L). The liver USS showed features consistent with HCC. Liver biopsy was done and the histology confirmed HCC co-existing with cirrhosis. While on admission she continued breastfeeding but this was stopped when it was noticed that the liver span had increased from 14 to 20 cm in less than 3 weeks!

Chemotherapy was commenced with IV Doxorubicin 50mg stat and 5-Fluorouracil 750mg IV daily for 1 week. However, she developed relentless, profuse diarrhoea with vomiting and went into hypovolaemic shock from which she died 25 days after admission.

DISCUSSION

On a worldwide basis, hepatocellular carcinoma (HCC) is known to be relatively uncommon in women compared with men. The tumour is even rarer in pregnant women and, indeed, females of reproductive age. Notable risk factors for the development of HCC in pregnancy include hepatitis B virus (HBV) infection and high parity⁵. These conditions are prevalent in sub-Saharan Africa and may explain why most reported cases of HCC in pregnancy have come from this region of the world^{7,8}. All the 4 women tested for HBsAg in this study (Cases 1, 2, 5 & 6) were positive and of the 4 women with known parity, 2 were grandmultiparous.

Maternal mortality has been found to be worse than foetal wastage. This has been confirmed in this study where 4 out of the 6 babies delivered were known to have survived. Apart from one case of discharge against medical advice, the disease was fatal in all the woman (Cases 1, 2, 4, 5 & 6). The major causes of death were hepatic failure and tumour haemorrhage. The latter is a common terminal event in pregnant women with HCC co-existing with cirrhosis^{5,7,9}. HCC developing on a cirrhotic liver has been known to exhibit neovascularity, arteriovenous shunting and/or venous encasement thereby increasing the susceptibility to bleeding¹⁰.

With the average duration of illness of 20 weeks, this study appears to support the finding that there may be no significant difference in the length of survival between pregnant and non-pregnant women with HCC^{7,11}.

The diagnosis of HCC was made in the postpartum period in 5 (Cases 1, 3, 4, 5 & 6) of the 6 women studied. However, 2 (Cases 1 & 3) of them had been symptomatic in pregnancy. Indeed the woman whose symptoms began before conception (Case 2) was the only one who could not carry her pregnancy to term. This shows that all those women who presented in the postpartum period may have had the tumour in pregnancy and that HCC may not be incompatible with normal pregnancy and delivery. This is contrary to the widely held opinion that cirrhosis (which often co-exists with HCC) renders a woman infertile. Infertility in cirrhotics may therefore be applicable mainly to those women with advanced decompensated cirrhosis^{12,13}.

The role of pregnancy and the female sex hormones on the progression of HCC has long been debated⁶. The relation of oral contraceptives with benign liver tumours has been established¹⁰. Some studies have reported an increased risk of non-cirrhotic HCC in women who use oral contraceptives for more than 8 years^{6,14}. The use of oral contraceptives does not appear widespread among our patients. None of the cases presented used this mode of contraception. The role of breastfeeding is much less clear. There was a rapid increase in the size of the tumour mass in 2 of our patients (Cases 3 & 6) who were breastfeeding their babies while on admission. Prolactin is the main hormone of lactation and its blood levels tend to increase dramatically in response to suckling¹⁵. Metabolic hormones such as cortisol, glucagon, insulin, adrenaline and thyroxine are also increased in the blood to meet the demands of lactation¹⁶. The metabolic demands on the liver by these hormones coupled with the stress of lactation and care of the newborn may result in the rapid deterioration of the diseased liver and hasten the presentation. It would therefore appear that breastfeeding is as much as risk factor for rapid HCC growth and rupture as pregnancy in women.

Women with the risk factors for HCC such as HBsAg seropositivity, compensated cirrhosis and multiparity should be screened regularly with Ultrasound and Alpha-fetoprotein assay. If the HCC happens to be detected early, a decision on the desirability of pregnancy or breastfeeding should be taken as both conditions may aid HCC progression.

Table 1. Age, HBsAg Status and Obstetric History of 6 Patients with HCC in Pregnancy and Postpartum Period

Case	Age (yr.)	Parity	HBsAg	Onset of Symptoms	Time of Diagnosis	Delivery	Baby
1.	30	Para 7 A5	Positive	1 week before delivery	18 days into puerperium	Normal	Alive & Well
2.	25	Para 1 A1	Positive	3 months before Conception	32 weeks gestation	By induction at 32 weeks	Fresh stillbirth
3.	37	Para 7 A7	Not done	3 months gestation	6 months post delivery	Normal	Alive & Well
4.	28	Not stated	Not done	7 months post delivery	10 months post delivery	Normal	Alive & Well
5.	22	Not stated	Positive	5 months post delivery	7 months post delivery	Normal	State unknown
6.	27	Para 1 A1	Positive	6 months post delivery	8 months post delivery	Normal	Alive & Well

Table 2. Outcome of Management of Patients with HCC in Pregnancy and Postpartum Period

Case	Cirrhosis	Treatment Given	Outcome	Autopsy	Probable Cause of Death
1.	Present	Supportive	Died	Not done	Liver failure
2.	Absent	Supportive; Induction of labour	Discharged against medical advice.	-----	-----
3.	Present	Supportive; Stoppage of Breastfeeding	Died	Not done	Intra-tumour haemorrhage & shock
4.	Present	None	Died < 24 hours after admission	Done	Intra-peritoneal haemorrhage & liver failure
5.	Present	Supportive	Died	Not done	Respiratory insufficiency & intra-peritoneal haemorrhage
6.	Present	Chemotherapy, Stoppage of Breastfeeding	Died	Not done	Hypovolaemic shock from profuse diarrhoea.

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