International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2020; 4(2): 04-06
Received: 02-01-2020
Accepted: 04-02-2020

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Hepatocellular carcinoma in pregnancy, a rare cancer in pregnancy that still occurrs - a review of the literature

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DOI: https://doi.org/10.33545/gynae.2020.v4.i2a.494

Abstract
Hepato-cellular carcinoma is a primary solid malignancy of the liver cells the origin of which is believed to be the hepatic stem cells. Though it is now considered to be the third leading cause of cancer deaths all over the world, its occurrence in pregnancy is very rare. However, it still occurs. Though the presentation could be dramatic, it is mostly vague and insidious in onset initially. The aim of this review is to attract attention to this rare condition that still occurs and initiate cum sustain a high index of suspicion by Obstetricians to enable early diagnosis when prognosis for treatment is better. A search was made with various search engines in obstetric and related literature using relevant key words. All the materials got were sorted out and analyzed.

Keywords: Hepatocellular, carcinoma, pregnancy, literature review

Introduction
Hepatocellular carcinoma is one of the world's foremost solid malignancies causing approximately one million deaths annually [1]. However, hepatocellular carcinoma in pregnancy is a very rare condition [2, 3]. Though, less uncommon in the female population, it is believed to have a worse prognosis in the pregnant than the non-pregnant woman. Some workers posit that morbidity and mortality have improved over time as diagnoses have tended to be made earlier and patients have received surgical and other treatment modalities [4]. Other workers have however reported a maternal mortality of one hundred percent with death occurring either antenatally or immediately postpartum. We present a review of literature on this rare cancer in pregnancy that is still occurring

Materials and methods
Searches were conducted through the medical literature published in English using the search engines: Google, PubMed, Ajol, Scopus, Hinari etc. using the words hepatocellular carcinoma in pregnancy, hepatoma in pregnancy, liver cell carcinoma in pregnancy. All the materials got were sorted out, relevant ones were organized and the literature reviewed.

Review of literature
Hepatocellular carcinoma is a Primary solid malignancy of the liver which cells of origin are believed to be hepatic stem cells [1]. Though now considered to be the third leading cause of cancer deaths all over the world with over 600,000 deaths annually [2], it occurs less commonly in women and very rarely in pregnancy [3, 4] with an estimated incidence of one in 100,000 [5] most of whom reside in Africa a Asia [6]. Fubara Seleye analyzed 75 cases of hepatocellular carcinoma in Port Harcourt, Nigeria but there was no single case of hepatocellular carcinoma in pregnancy they found [7].
Seaward *et al.* [3] in 1986 reviewed five cases in the literature and reported another as the sixth. Ozoh *et al.* reported the third case in Africa in 1992 [8]. In a comprehensive review by Lau *et al.* in 1995 [6] they reported five cases and analyzed an additional 23 cases reported in literature. Since Roddie's first report of a case of hepatocellular carcinoma in pregnancy in 1957 [9], Choi *et al.* [10] in 2011 reported four cases and analyzed another 44 cases they could find in the literature making their series the 48 cases reported all over the world up till 2011.

Our search through the literature from 2011 till date only revealed an additional 8 cases bringing the total number of reported cases of hepatocellular carcinoma all over the world in English Literature to 56.

The rarity of hepatocellular carcinoma in pregnancy has been attributed to many factors [11, 12]. First, is that this cancer occurs more in the male population than females of all population [6]. It is even less uncommon; indeed, rare in females of reproductive age. It is estimated to occur in only 2.3% of females of reproductive age in the work done in Hong Kong and in only 4.3% in a study done in United Kingdom [6]. Another reason accounting for its rarity in pregnancy is because infertility is associated with cirrhosis especially at the late stages, and cirrhosis is associated with the causation of this cancer. This association of cirrhosis with infertility is however relative as some women with cirrhosis have been known to get pregnant. The association is however more with advanced cases of cirrhosis.

Hepatocellular carcinoma has accelerated course in pregnancy than in the none pregnant women [13, 14, 10] with some works attributing almost 100% maternal and fetal mortality to it [15]. However, recent literature show that the prognosis is better now with a fetal rate survival of 57% [10, 16] and this has been attributed to earlier diagnosis and application of different treatment modalities including surgical resection of the tumors [17, 19].

In their work comparing the effect of this carcinoma in pregnancy before and after 1995, Choi *et al.* [10] found an older mean age at presentation of 31.4 + or - 7.2 years before 1995 and 28.9 ± 4.4 years after 1995. This means that it is now occurring in younger women. Ndububa *et al.* [15] in Nigeria found Hepatocellular carcinoma to occur in an age range from 22 to 37 years with a mean age of 28.2 years.

Hepatocellular carcinoma has a distribution that typically follows the prevalence of hepatitis B and C viruses. It is commoner in the Asian and sub-Saharan Africa countries than the Western countries [20]. A third of the cases are found in China and another third in the rest of Asia [21]. The high prevalence of Hepatitis B virus carrier in Eastern Asia and sub-Saharan Africa (5-10%) [22] has been implicated for this distribution pattern of the disease. Ndububa *et al.* reported a series of 5 cases in Ile Ife, Western Nigeria [15] while Egwuatu [23] and Umeora *et al.* [2] reported a case each in Eastern Nigeria and Sani *et al.* [25] a case from Northern Nigeria.

The risk factors for hepatocellular carcinoma in pregnancy include race – being an African or Asian especially Chinese is more likely to predispose a pregnant woman to this carcinoma, Hepatitis virus infection (both B and C), cirrhosis of the liver, non-alcoholic fatty liver disease, associated obesity and type 2 diabetes mellitus [5], aflatoxin, alcohol, combined oral contraceptives pills [26] and increasing parity [27], family history [10, 28] late menopause [29], early menarche [30] etc. Oral contraceptive pills as a risk factor is controversial [10]. It is however important to note that some women who have hepatocellular carcinoma in pregnancy do not have any of these risk factors [29].

Hepatocellular carcinoma is more aggressive in the pregnant than the non-pregnant woman with an overall one-year survival of only 23% [5]. This is attributed to the increased levels of estrogen in pregnancy which accelerates the growth of hepatocellular carcinoma and the immune suppression that occurs in pregnancy [27] The association of estrogen with aggressiveness of hepatocellular carcinoma in pregnancy may be due to its known functions in increasing hepatocyte mitosis, hypervascularity, free radicals, reactivation of hepatitis B virus and decreased humoral immunity [16, 25]. Other authorities even think that other pregnancy hormones like large amounts of human chorionic gonadotropin and placental lactogen secreted by the placenta aid estrogen in this aggressive growth of this cancer in pregnancy by promoting growth and reproduction of cancer cells [13, 31, 32]. It is noteworthy that some authorities disagree with this role of estrogen and other pregnancy hormones in the aggression of hepatocellular carcinoma in pregnancy [19].

The diagnosis of hepatocellular carcinoma in pregnancy can be difficult as it may be asymptomatic [30] especially in the early stages. At times it can be discovered incidentally on abdominal examination or in response to the patient complaining of upper abdominal pain or incidental finding of a liver mass on ultrasonography might be the only finding that might lead to the eventual diagnosis of the disease. Diagnosis therefore calls for a high index of suspicion on the part of the Obstetrician. Also diagnosis during pregnancy is difficult because many of the physiologic symptoms of pregnancy such as fatigue, nausea and vomiting can be similar to those of hepatocellular carcinoma especially at the early onset [3, 34]. Also, as pregnancy progresses, a palpable liver mass may become less evident[4] contributing to difficulty in diagnosis.

In symptomatic cases, the commonest presenting symptom is right upper quadrant abdominal discomfort or pain [19, 29] Presence of a mass in the upper abdomen, weight loss and hepatomegaly have been the most frequent presentation [30]. Jaundice occurs in 5 to 44% of patients with hepatocellular carcinoma [34, 35]. Hepatocellular carcinoma in pregnancy can be discovered by detecting very high level of alpha fetoprotein in the blood. Patients may also present with tumor rupture [6] which is a life–threatening complication. It is estimated that about 10% of Hepatocellular carcinoma during pregnancies are complicated by tumor rupture [6, 16, 18]. This predisposes to hemorrhage.

At times investigations may not be helpful in making a diagnosis as liver function tests and maternal alpha fetal protein levels may be normal[3,34] or only slightly elevated. Although alpha fetoprotein may be markedly elevated in some cases of HCC, its being elevated in pregnancy [4] and in other conditions renders its use in the diagnoses of HCC further confusing and unhelpful. Some studies have shown that about 10% of pregnant women can have HCC with normal alpha fetoprotein levels [30]. Other laboratory abnormalities like hyperbilirubinemia, prolonged prothrombin time, hypoalbuminaemia have been reported in less than 10% of previous studies [10]

Ultrasonography is very important in making diagnosis [4] as it detects hepatic mass and can to some extent help in characterizing hepatic pathologies in ways that can help raise enough suspicion to warrant further investigations and enable the taking of steps that will enable biopsies to be taken and pathology confirmed. It is indispensable in early diagnosis which offers much hope in these patients for early resection where possible and this has improved survival. CT or MRI are helpful in diagnosis. However, they pose diagnostic dilemma in pregnancy as contrast enhanced imaging in pregnancy is usually avoided owing to concerns of adverse effects on the fetus [13].

Available treatment for HCC in pregnancy includes liver resection which has now been accepted as the main stay of treatment and the gold standard [4, 17, 18, 26]. This makes the need for obstetricians having a high index of suspicion and early diagnosis very compelling. Other treatment modalities include chemotherapy, radio frequency ablation, ethanol injection etc. [4]. Treatment should be multi- disciplinary. Any treatment modality must take into consideration the mother and the baby. Most authorities will prefer termination of pregnancy in the first

trimester to enable the mother benefit from full treatment. Around the mid and early third trimester consideration may be given to allowing the pregnancy to viability before delivering the mother. In the mid trimester some authorities favor liver resection where possible with preservation of the pregnancy [4].

Adjunctive treatment before delivering the baby like giving surfactants or steroids for fetal lung maturity is important. At term the mother should be delivered so that she could receive the full benefits of any treatment modality that could be offered to her. Whichever modality of treatment that is being considered, the mother must be fully involved and she should be continuously supported in any treatment option she chooses.

Though the prognosis of HCC in pregnancy is poor and some series had noted 100% maternal mortality [22], recent review of literature has shown poor but improving survival rates over time.[10] This improvement in survival rates has been attributed to early diagnosis of the cases and surgical resection of the tumor [10, 32].

It is true that HCC in pregnancy is a very rare disease which before now was associated with almost 100 percent mortality, health workers especially those saddled with women's health should develop a very high index of suspicion and endeavor to detect and evaluate any hepatic mass or symptoms of HCC early and properly. This is very germane as early diagnosis is key to any hope of survival in these women.

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