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MINIREVIEWS

Hepatitis B and pregnancy: An update review article

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Abstract

Chronic hepatitis B, as a global health problem, is a disease that begins in the prenatal period and its complications gradually become clear later in life. About 5% of women worldwide are carriers of chronic hepatitis B virus (HBV). The most common method of transmission of HBV around the world is from mother to infant. This article aims to review the unique challenges of hepatitis B in pregnancy. Data for this review were collected from our previous studies and experiences plus various data banks, such as PubMed, EMBASE, ISI Web of science, Scopus, Google Scholar and Iranian databases. A comprehensive search was performed using the combinations of the keywords to review relevant literature and higher education journals. All published data up to February 2014 have been included in this review. This article addresses several interesting aspects. First, hepatitis B in pregnancy can vary regarding prevalence, virus behavior, prenatal transmission and outcome of the pregnancy. Second, the women of reproductive age with chronic HBV remain a major source for continued spread of the virus. Finally, pregnant women need screening in prenatal care to enable early intervention when necessary.

Key words: Hepatitis B; Pregnancy; Screening; Prenatal transmission; Treatment

Core tip: Chronic hepatitis B is a global health problem. About 5% of women worldwide are carriers of chronic hepatitis B virus (HBV). The most common method of transmission of HBV around the world is from mother to infant. We are gathering an increasing amount of interesting aspects to accurately describe the unique challenges of hepatitis B in pregnancy. This article addresses hepatitis B in pregnancy which can vary regarding prevalence, virus behavior, prenatal transmission, screening and outcome of the pregnancy.

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INTRODUCTION

Hepatitis B is a global health problem[1] and the leading cause

of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma[2]. The World Health Organization has announced that Hepatitis B, after smoking tobacco, is the second most important human carcinogen[3]. Hepatitis B is 50 to 100 times more contagious than the human immunodeficiency virus (HIV)[4] and Americans are suffering from it four times more than HIV. Given that one out of every 15 people worldwide has hepatitis B, it has become the most common blood borne infectious disease in the world[5]. According to estimates, around 2 billion people worldwide are infected by the hepatitis B virus (HBV) and about 360 million live with chronic infection, while at least 600 thousand people lose their lives per year due to acute or chronic consequences of hepatitis B[4]. Iran is located in the Middle East region and according to the centers for disease control and prevention, it has an average prevalence of chronic HBV[6]. Chronic hepatitis B is a disease that begins in the perinatal period and its complications gradually become clear later in life[7]. About 5% of women worldwide are carriers of chronic HBV[8]. The most common method of transmission of HBV around the world is from mother to infant and this infection might occur during the intrauterine or perinatal period[1]. HBV prevalence in pregnant women is approximately 5% and this varies from 0.6% in low prevalence areas to over 20% in areas with a high incidence in the Far East and Africa[9]. This article aims to review the unique challenges of hepatitis B in pregnancy.

SEARCH STRATEGY

Data for this review were collected from our previous studies and experiences plus various data banks, such as PubMed, EMBASE, ISI Web of science, Scopus, Google Scholar and Iranian databases including Iranmedex and SID. A comprehensive search was performed using the combinations of the keywords "Hepatitis B, pregnancy, prenatal transmission, vaccination, treatment" to review relevant literature and higher education journals. The searches were done by using Boolean operators OR, AND between main phrase and the mentioned keywords were extracted from specific themes of the topic under study. A search strategy was built, applying the advanced search capability of the search engine. The inclusion criteria as set out was that only articles that explicitly dealt with Hepatitis B in pregnancy were included. We also looked at the reference list of the retrieved papers and searched other search engines. A total of 150 articles were found in the primary search but after elimination of duplicates or irrelevant papers, only 60 records were reviewed. All published data from 1999 to 2014 have been included in this review.

RESULT

Natural history of HBV

HBV can exist in many body fluids such as blood, saliva, semen and vaginal fluid. The virus can survive outside the body for more than 7 d. So, if scratched skin is in contact with an infected surface, infection occurs. When hepatitis B infection occurs, the patient enters the incubation period which is asymptomatic and the patient is usually unaware of the infection. During this period, liver transaminases are normal. Although the factors that affect the length of the incubation period are perhaps unknown, probably factors such as the size of HBV, the binding ability of cell surface receptors to the virus and the host immune system are involved. The incubation period may be as long as 2 to 6 mo with an average of 60 d[10]. The clinical appearance of hepatitis B infection varies depending on the age and the host immune system. Children under 5 years and adults with weakened immune systems are asymptomatic. Only 30% of people with acute infection will develop jaundice. Jaundice may be mild or severe, depending on the host's immune system. The final phase of chronic HBV infection is recovery, in which transaminases are decreased and the clinical signs are lowered. Viral hepatitis is an inflammatory widespread phenomenon which can cause acute or chronic liver damage. The main mechanisms of hepatocyte injury are unclear although specific and nonspecific antigens are involved in hepatocyte injury. Evidence suggests that the characteristics and clinical outcomes after acute liver injury are associated with viral hepatitis and are determined by immunological responses of the host. Outcome of HBV infection varies from full recovery to progression to chronic hepatitis and death from fulminant hepatitis is rarely seen[11-13].

Natural history of HBV in pregnancy

In areas of high prevalence, most patients with chronic HBV are women of reproductive age[14]. Transmission from mother to fetus during prenatal or horizontal transmission in childhood are the main ways of transmission of HBV in areas with a high and moderate prevalence. Also, in areas with low prevalence, unsafe sexual activity is the most common way of transmission[15]. Therefore, women of reproductive age are considered an important source of infection[16]. Risk factors for chronic HBV carriers in the reproductive age population are unknown. The factors associated with chronic carrier status include resident status, positive family history, no history of previous vaccination and previous hepatitis B surface antigen (HBsAg) testing[17]. Chronic HBV infection is likely to be a significant cause of infertility. HBV infection reduces fertilization ability during *in vitro* fertilization and embryo transfer[18]. The clinical course of HBV infection does not change during pregnancy and usually there is no difference in pregnant and nonpregnant women. It has been identified that hepatitis flares occur rarely during pregnancy, while its indices increase after delivery. There are controversies regarding the disease complications in pregnant women and fetuses. Some believe that chronic carriers of HBV in pregnancy are associated with increased rates of miscarriage, gestational diabetes and preterm labor[19]. The assessment of fetal distress in pregnant women with HBV showed that HBV infection can cause chorion angiopathy and decrease placental function, leading to fetal distress[20]. Available information indicates that HBV transmission

via the placenta is not as common as previously thought; actually, viral DNA is rarely found in amniotic fluid or cord blood[5]. Most infant infection in the womb is caused by the mother's blood transfusion to the fetus during uterine contractions or rupture of fetal membranes[8] or by vertical transmission perinatally by exposure to blood or secretions of an infected birth canal of the mother[21]. It is estimated that 50% of cases of chronic hepatitis B are results of vertical transmission or acquired in early childhood[8]. The mechanisms through which HBV infections are transmitted in the uterus are controversial and being reviewed. Some of these assumptions include transmission through the placenta, transfer through placental leakage, cracks in the placental barrier, mononuclear cells in peripheral blood and transmission through the father[22]. Intrauterine transmission of HBV infection occurs *via* two pathways: (1) blood release (hematogenous) that causes the infection of placental vascular endothelial cells and is probably the main route for infection transmission; and (2) cellular transport through cell by cell. One of the explained mechanisms of the intracellular transport route is binding of HBsAg-anti-HBsAb with Fc-γ receptor Ⅲ[10].

A study of 402 infants of HBsAg-positive mothers showed that the risk of intrauterine transmission depended on HBeAg-positive mothers and virus existence in vascular endothelial cells in chorionic villi[23]. The most important risk factors for mother-to-child transmission (MTCT) include: HBV DNA > 200000 IU (106 copies)/mL, HBeAg positive and pregnancy complications such as preterm delivery, prolonged labor and prior failure of immunoprophylaxis in sibling(s). Antiviral therapy in the last stages of pregnancy is the most effective way to reduce transmission of infection from the mother. Besides, elective cesarean delivery can reduce the risk of transmission[24]. The prevalence of HBV infection in infants and children are different depending on race and ethnicity, with Asian women having the highest prevalence (6%)[25].

MTCT

Hepatitis B virus can be integrated in the placenta, leading to the infection. In Wang's study of 15 HBeAg-positive mothers and their babies, he revealed that HBeAg actually crosses the human placenta. In the case of simultaneous TORCH (Toxoplasmosis, Other Agents, Rubella, Cytomegalovirus, Herpes Simplex) infections that can cause placental cracks or a damaged placental barrier, neonatal HBV infection further increases. Also, HIV infection increases the risk of transmission of HBV infection[26]. In another study, Elefsiniotis *et al*[27] examined serological and virological profiles of cord blood samples taken from mothers with negative HBeAg and revealed that in almost a third of these mothers, HBsAg, despite maternal viral load, HBV pathology and type of delivery, can pass through placental barrier. Chronic HBV in pregnant women is usually mild but the disease may flare up shortly after birth[28]. HbsAg-positive mothers that are also HbeAg-positive are more likely to transmit the disease to their infants (70% to 90%), while the HbsAg-positive and HbeAg-negative mothers have a lower infection transmission rate[21]. The risk of transmission in HbeAg-negative mothers is 10% to 40% and in affected infants, 40% to 70% of the infection becomes chronic[25].

Although infection in HbeAg-negative mothers occurs less commonly, infants in early periods of infancy often progress to acute or fulminant hepatitis. So, despite the HBeAg/Ab status of the mothers, prevention in infants is necessary[29]. The transmission rate in pregnant women with a positive serum viral DNA is 90%, while for pregnant women with negative viral DNA it was reported to be 10% to 30%[30,31]. Hepatitis B vaccine is safe for pregnant women in each trimester and those who are seronegative can be vaccinated during pregnancy. Serum level protection in pregnant women is only 45%. This is lower than that mentioned for nonpregnant women as well as for women during the postpartum period that had received three doses of the vaccine[32]. Vaccination during pregnancy, in addition to being beneficial for the mother, also provides partial immunity for the infant[33]. Studies showed that a maternal prenatal screening program and active and passive immunization of infants after delivery significantly decreased HBV infection to 95%[34]. Most infections of pregnant women are chronic and asymptomatic and are diagnosed in prenatal screening. These women are considered to have chronic hepatitis but antiviral therapy is generally not performed during pregnancy[3]. Perinatal HBV transmission accounts for about 21% of HBV-related deaths worldwide and 13%-26% regionally[35]. HBsAg was found to be positive in 50% of cord blood and 95% of gastric fluid samples of infants of HbsAg-positive mothers. During labor, the infant is in contact with the mother's blood which contains the virus and it is possible for him to swallow contaminated fluids, enabling neonatal infection by physiological transfusion or blood contact and the mother's birth canal secretions[10,36].

Global hepatitis B disease burden and impact of vaccination

Safe and effective vaccines have been available to prevent HBV infection since 1981 and the cost-effectiveness of hepatitis B vaccination has been well documented[37]. A study performed in Iran by Alavian[38] showed a significant reduction in the rate of HBsAg positivity in the subgroup of children aged 2-14 years after expanding the immunization program. HB vaccine can be fully justified on economic grounds in that either the cost-benefit ratio is positive or the cost-effectiveness ratio suggests the vaccine to be a good "buy" for the public health services or both[38]. Several studies have implicated high maternal viremia as the most important factor associated with failure of neonatal vaccination[39]. The key strategy to decrease mortality from HBV is to prevent infants from acquiring HBV infection. The Advisory Committee on Immunization Practices (ACIP) recommends that all newborns receive their first HB vaccination before hospital discharge[2]. For infants born to HBV-infected women, administering ACIP-recommended post-exposure prophylaxis of hepatitis B immune globulin (HBIG) and

HB within hours of birth followed by completion of the HB series has been shown to be 85%-95% effective in preventing HBV infection[40] .

From a few reported trials, HB vaccine and HBIG seem safe. Furthermore, cohort studies found that HB vaccination is well tolerated and that severe adverse events are rare[21]. One systematic review showed that HB vaccine, HBIG and vaccine plus immunoglobulin prevent hepatitis B occurrence in infants of mothers positive for HBsAg[21]. In a follow up study of 184 infants born to HBsAg carrier mothers, Wang *et al*[41] found that after infants were immunized by HBIG combining HB vaccine, the anti-HBs-positive rate reached 92% at 7 mo and gradually decreased thereafter. 72.04% of the infants at 24 mo and 60% at 36 mo showed detectable levels of anti-HBs[41]. Cost effectiveness studies showed that in countries with low, intermediate and high HBV prevalence, vaccination of infants of HbsAg-positive mothers had numerous advantages[21]. Infants who are infected with hepatitis B are generally asymptomatic but 90% of them develop chronic infection[42]. Coadministration of specific immunoglobulin and HB vaccine is highly effective in preventing infection. However, approximately 10% to 20% of infants are still chronically infected despite receiving this treatment in their early life. Intrauterine infection is the leading cause of HB vaccine failure in infants born to mothers with HBV[34].

Without immunoprophylaxis, up to 90% of infants born to HBeAg-positive mothers become HBV carriers. In comparison, 20% to 30% of children infected between the age of 1 to 5 years and fewer than 5% of immunocompetent adults become HBV carriers[43]. Intrauterine HBV infection has been suggested to be caused by transplacental transmission that cannot be blocked by the HB vaccine[23]. In a case-control study of 402 HBs Ag-positive pregnant women in China, Xu *et al*[23] found that 3.7% of their newborn were HBs Ag positive within 24 h of birth. The main risk factors for intrauterine HBV infection were maternal serum HBeAg positivity, history of threatened preterm labor and HBV in villous capillary endothelial cells in the placenta.

Joint immunoprophylaxis with HBIG and three doses of HB vaccines to infants born to HBsAg-positive mothers are known to be safe and effective. However, 5%-10% of infants of HBV-positive mothers become infected even with proper vaccination[21]. There are some cases of vaccination failure. Very high maternal viremia, intrauterine infection or escape mutants after the implementation of the universal vaccination program are possible reasons for vaccination failure. Immunocompromised hosts also risk vaccination failure[7]. Hence, health care providers must consider the maternal HBV DNA level in decision making regarding management options during pregnancy[25].

Treatment of HBV during pregnancy

HBV treatment in pregnancy is complicated[43]. For women with HBV who have intentions of becoming pregnant, treatment can be postponed in cases of mild disease until after delivery. In cases of moderate or severe disease or getting pregnant during treatment, it is necessary that the potential risks of treatment with antiviral drugs be evaluated against the risk of disease progression in the case of no treatment[19]. Pregnant women with low viral loads do not need immediate treatment, while for severely viral mothers (> 10^9 copies/mL), antiretroviral therapy in the last trimester of pregnancy should be considered[44]. Management of HBV treatment in pregnancy is unique. Aspects of care and treatment that need to be taken into consideration include: HBV effects on pregnancy; pregnancy effects on HBV and its complications; HBV treatment during pregnancy; and prevention of perinatal HBV infection[28]. Zhang *et al*[45] assessed the effects of telbivudine on HBV intrauterine infection during the last phases of pregnancy in 61 pregnant women and found that serum HBV DNA levels in patients treated with telbivudine were significantly lower than the control group ($P < 0.01$). Infection rate was reported to be 0% in infants receiving telbivudine and 13.3% in the control group. These researchers stated that treatment of HBV-infected mothers with telbivudine can block intrauterine infection[45].

Another study evaluating the effectiveness and safety of using HBIG during pregnancy to prevent mother to child transmission showed that infants of mothers receiving HBIG were less infected by intrauterine infection (indicated by HBsAg as OR = 0.22; indicated by HBV DNA as OR = 0.15; $P < 0.01$ for both) and a high level of safety and protection was observed in them (indicated by HBs Ab as OR = 11.79; $P < 0.01$)[46]. A randomized trial on interrupted HBV intrauterine transmission estimated that repeated HBIG injections to pregnant women before the delivery may block the HBV intrauterine infection by reducing the level of viremia[34]. Numerous studies reported that treatment with lamivudine in highly viral pregnant women prevents HBV replication. In the recent study, lamivudine (100 mg/d) therapy was administered to pregnant patients with HBV who had levels of HBV DNA greater than 10000 copies/mL after the 32nd gestational week. A 102 decrease in HBV viral load was observed in 71% of the patients[47].

Safety of medications used during pregnancy and lactation, the effect of the chosen drug, resistance to treatment, side effects and duration of the treatment are factors that should be considered in the treatment of pregnant women with hepatitis B. If delivery takes place in the near future, it is wise to delay treatment until after the delivery[48,49]. In women at high risk or with known HBV infection who want to be pregnant, it is necessary to determine the exact status of the disease so that an appropriate treatment plan can be scheduled. A therapeutic approach to hepatitis B during pregnancy involves three basic strategies as follows: (1) screening pregnant women and performing a routine HBsAg test at the first prenatal visit; (2) treatment of HBV infection in pregnant women; and (3) prevention of mother-infant transmission[3,25] (Figure 1).

Counseling and prenatal care in hepatitis B

Since health status during pregnancy depends on the

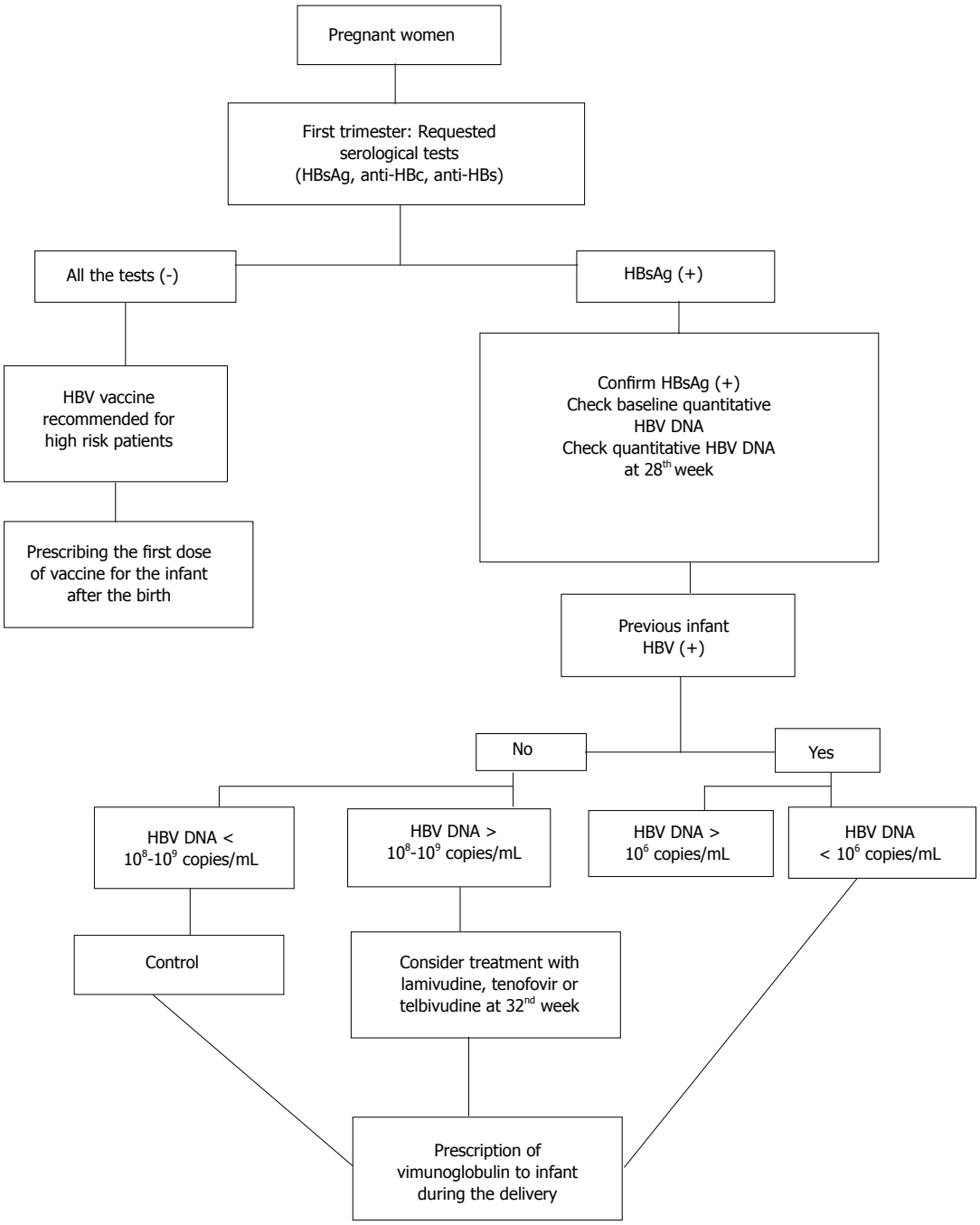

Figure 1 Hepatitis B virus treatment algorithm during pregnancy[43,44,50]. HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; anti-HBc: Hepatitis B core antigen.

health status before it, pre-pregnancy counseling and care of patients with hepatitis should be an essential part of the patient's training. A comprehensive plan of care before pregnancy can help in reducing the risks, promoting healthy life styles and increasing preparation for pregnancy. Principles of pre-pregnancy counseling should include the following[51]: (1) high risk women should be screened and can be vaccinated against hepatitis B[52]; (2) the test for hepatitis B has been confirmed to be negative before starting the anonymous donor oocyte *in vitro* fertilization sequence[53]; (3) infected women should be counseled regarding the risks of the disease and transmission; (4) patients with hepatitis B should be referred for treatment before becoming pregnant; (5) before starting treatment, request a β-hCG test for the patient to ensure she is not pregnant since some drugs used to treat hepatitis are teratogenic for the fetus; (6) explain about effective contraceptives to suit each individual ; and (7) remind women not to take oral contraception, because their estrogenic effects on the liver are unknown[32].

It is important to consider a comprehensive health care program that includes an integrated approach to medical and psychosocial care for pregnant women with hepatitis B. Accurate and detailed information should be

obtained from the pregnant women regarding the history of previous delivery, using alcohol and drugs during pregnancy, serological hepatitis B test and immune status of the pregnant women. Monitoring the health status of the fetus and determining the next prenatal visits based on the patient's condition are among the other prenatal care needed. Although nutrition knowledge attempts to identify the ideal amount of nutrition groups for pregnant women, people who are directly responsible for the care of mothers with hepatitis B can perform their duties in the best way[54-56].

Breast feeding and hepatitis B

Breastfeeding is the foundation of infant nutrition and sets the scene for lifetime health. The World Health Organization recommends that all mothers who are hepatitis B positive breastfeed their infants and that their infants be immunized at birth[57]. A recent meta-analysis review reported breastfeeding after proper immunoprophylaxis did not contribute to mother-to-child transmission of HBV[58]. Mothers with hepatitis B are advised to pay attention and check the nipples before each feed and in case of any cracks, bleeding or any kind of blood on the nipples, to temporarily stop breastfeeding and express all the milk and discard it. When the nipples are healthy without any cracks, the milk should be expressed, kept in good condition and given to the infant at the time of cessation of breastfeeding. The mother should learn the correct way of breastfeeding and embracing the infant so that an uncomfortable position does not cause the infant to refuse breastfeeding. During teething, caution should be taken so that the nipple is not wounded and a milk bottle can be used at this time. To prevent mother to child transmission, the following actions are recommended: educate the mothers; isolate HbsAg-positive mothers during labor; clean blood and secretions from the infant's body; and active and passive immunization of infants soon after birth[59,60].

CONCLUSION

This article discusses the unique challenges of hepatitis in pregnancy and addresses several interesting aspects. First, hepatitis B in pregnancy can vary regarding prevalence, virus behavior, prenatal transmission and outcome of the pregnancy. Second, the women of reproductive age with chronic HBV infection remain a major source for continued spread of the virus. Finally, pregnant women need screening tests directed at virus detection in prenatal care to enable early intervention when necessary. In addition, we would like to control perinatal transmission and reduce the numbers of new carriers as much as possible with immune prophylaxis after delivery.

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ORIGINAL ARTICLE

Case control study

High prevalence of post-partum depression in women with coeliac disease

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Abstract

AIM: To explore the prevalence of post-partum depression (PPD) in coeliac disease (CD).

METHODS: We performed a case-control study evaluating the prevalence of PPD in CD patients on gluten-free diet (GFD) compared to that of healthy subjects experiencing a recent delivery. All participants were interviewed about menstrual features, modality and outcome of delivery and were evaluated for PPD by Edinburgh Postnatal Depression Scale (EPDS).

RESULTS: The study included 70 CD patients on GFD (group A) and 70 controls (group B). PPD was present in 47.1% of CD women and in 14.3% of controls ($P < 0.01$; OR = 3.3). Mean EPDS score was higher in CD compared to the controls (mean score: group A 9.9 ± 5.9; group B 6.7 ± 3.7; $P < 0.01$). A significant association was observed between PPD and menstrual disorders in CD (69.7% *vs* 18.9%; $P < 0.001$; OR = 3.6).

CONCLUSION: PPD is frequent in CD women on GFD, particularly in those with previous menstrual disorders. We suggest screening for PPD in CD for early detection and treatment of this condition.

Key words: Coeliac disease; Depression; Post-partum depression; Menstrual disorders; Gluten-free diet

Core tip: Some studies have shown an increased prevalence of psychological symptoms and mental disorders in patients affected by coeliac disease (CD) and depression appears to be the most important condition in undiagnosed CD. On the other hands, focused data on post-partum depression are still lacking. In our mind, the present work is the first study mainly focused on this interesting and relevant topic.

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INTRODUCTION

Coeliac disease (CD) is a chronic small intestinal immune-mediated enteropathy precipitated by the exposure to dietary gluten in genetically predisposed individuals[1,2]. CD is the most common cause of enteropathy in the western world and affecting around 1% of the general population in both children and adults[3].

Gluten consumption in these susceptible individuals leads to small bowel damage and the activation of immune responses which cause both intestinal and extra-intestinal manifestations of the disease.

About clinical features, as reported in a recent article by Ludvigsson *et al*[1], classical CD is characterized by signs and symptoms of malabsorption (diarrhoea, steatorrhoea, weight loss, *etc.*), while non-classical CD presents with anaemia, osteopenia/osteoporosis, recurrent abortions, hepatic steatosis, dental enamel hypoplasia, hypertransaminasemia, recurrent aphthous stomatitis.

At present, CD diagnosis requires first of all a serological screening of patients with suspected CD using anti-tissue transglutaminase (a-tTG) and anti-endomysial antibodies and then, a duodenal biopsy to assess the intestinal damage in patients with positive serology[1].

Many studies have shown an increased prevalence of psychological symptoms and mental disorders in patients affected by CD and depression appears to be the most important condition in undiagnosed CD[4-7]. In effect, Addolorato *et al*[8] reported that the prevalence of depression in CD patients was significantly higher than in the control group (57.1% *vs* 9.6%). In addition, recent reports have revealed a high prevalence of anxiety and sleep disorders in coeliac patients, so confirming the importance of exploring and treating mental aspects in this particular population[8,9].

Post-partum depression (PPD) affects 10%-15% of new mothers being the most common complication of pregnancy in developed countries[10,11]. This condition is often unrecognized and when left untreated can be associated with potentially adverse consequences for the mother, her infant, and her family. In particular, PPD can lead to disruptions in maternal-infant interactions, and lower cognitive functioning and behavioural problems in children[12,13]. Even if PPD is underdiagnosed, a number of important risk factors (past depression, stressful life events, poor marital relationship, and social support) have been described and can be utilised as helpful risk factors for suspecting development of the condition[14-16].

On the basis of these assumptions, consideration should be given to screening for PPD, although evidence in support of universal screening tools is lacking. However, women with known risk factors for PPD may be selected for screening[17,18]. At present the most utilised tool for screening PPD is the Edinburgh Postnatal Depression Scale (EPDS) which consists in a 10-item self-rated questionnaire with a diagnostic cut-off of 10 (or greater) for possible PPD[19-22] even though the sensitivity and specificity varies across languages and cultures[23].

Even if many studies have clearly shown the high prevalence of depression and other mental disorders in CD, specific data on PPD in CD women are still lacking.

Aim of this study was to explore the prevalence of PPD in women suffering from CD compared to that recorded in healthy subjects.

MATERIALS AND METHODS

We performed a case-control study evaluating the prevalence of PPD in CD patients on gluten-free diet (GFD) in comparison with a control group of healthy subjects.

Between June 2010 and February 2013 we enrolled all coeliac women (Group A) followed-up at our Gastrointestinal Unit (tertiary centre for food intolerance and CD) who had given birth within the 8-wk period preceding their appointment at the Unit and had been on GFD for at least 1 year before pregnancy. CD patients were also classified in accordance with Oslo classification[1]. A group of consecutive healthy women who had given birth in the previous 8 wk were also recruited at two first-line obstetric Clinics as control group (Group B). The clinical interview was conducted postnatally by gastroenterologists not blinded on the clinical/pathological state of the subject. All women (CD patients and controls) with a diagnosis of active depression (based on DSM-IV criteria) formulated at least 3 mo before starting pregnancy and those already on treatment with anti-depressant drugs were excluded from the study.

A gynaecological evaluation explored menstrual cycle features, potential comorbidities, mode and outcome of delivery. Menstrual disorders were defined in presence of amenorrhea, dysmenorrhoea, pre-menstrual syndrome, polymenorrhea and oligo-menorrhea in accordance with the gynaecological literature[24,25]. All women underwent a conventional serological evaluation comprising the detection of tissue anti-transglutaminase antibodies level.

All participants were assessed blinded for PPD through clinical interview using the EPDS[19-22].

Furthermore, quality of life as defined through the SF-36 questionnaire was examined in all patients and controls[26-29].

All patients gave their written consent to participate in the study that was approved by local Ethical Committee.

Screening for PPD

EPDS is a 10-item (scored on a scale of 0-3) self-reported scale assessing the symptoms of PPD. This questionnaire has been validated also in Italy[30] so that we were able to use it for the population in our study with high values on diagnostic accuracy. EPDS is routinely used in many

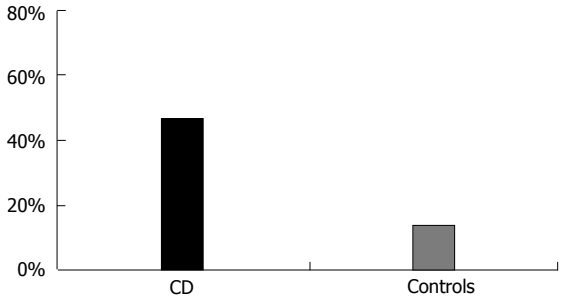

Figure 1 Prevalence (%) of positive Edinburgh Postnatal Depression Scale for post-partum depression in coeliac disease women and controls.

clinical services to screen for probable distress in women, both antenatally and postnatally, with a diagnostic cut-off ⩾ 10 (sensitivity 96%; specificity 92%)[31]. On these grounds, we established a cut-off ⩾ 10 as highly indicative of possible PPD. CD patients and controls with a EPDS ⩾ 10 were referred for psychiatric assessment. The screening for PPD was performed by an interviewer using the EPDS score with a ⩾ 10 cut-off and a clinical interview performed by an expert psychiatrist according to the DSM IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision).

SF-36 questionnaire

The SF-36 survey consists of a 36-item questionnaire that includes eight components: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional and mental health issues. These eight domains form two broader health dimension scales: the physical (PCS) and mental (MCS) component scales. The SF-36 subscales and composite scores can be summarised through means ± SD, with higher scores indicating better health and well-being. Low scores on the PCS indicate limitations in physical functions and general health, and/or physical pain, while higher scores suggest no physical limitations, disabilities, or reductions in well-being. Similarly, low scores on the MCS suggest frequent experience of difficulties in psychosocial health, emotional problems and reduced vitality, while high scores indicate frequent positive affect and vitality, the absence of psychological distress and reduced or no limitations in daily social activities[26-29].

Sample size and statistical analysis

We estimated that a sample size of 67 participants would be able to offer a 80% power to detect a 20% difference between the two groups (when assuming a known PPD prevalence of 13% in general population)[10,11].

Statistical analysis was performed by using χ^2, Mann Whitney *U* test and odd ratio (OR) calculation when indicated; differences were considered significant with a $P < 0.05$. All statistical analyses were performed with software package SPSS for Windows (Rel SPSS 14.0; SPSS Chicago, IL).

Table 1 Demographic and serological features of patients with coeliac disease and controls

	Group A Celiac women (# 70)	Group B Healthy subjects (# 70)	*P* value
Mean age (yr)	33.32 ± 2.88	32.32 ± 4.32	0.7
Level of instruction (yr)	11.06 ± 3.54	11.30 ± 3.58	0.9
Hb (gr/dL)	11.03 ± 2.46	11.21 ± 2.54	0.7
Cholesterol (mg/dL)	156.85 ± 35.82	149.68 ± 37.02	0.2
Anti-transglutaminase IgA (U/mL)	< 0.1	< 0.1	0.9
Type of childbirth			
Delivery by caesarean section	36/70	31/70	0.7
Vaginal delivery	34/70	39/70	0.7
Outcome of birth			
Live birth	70/70	70/70	1.0
Congenital malformations	0/70	1/70	0.9
Number of pregnancies			
First pregnancy	34/70	37/70	0.7
Second pregnancy	25/70	24/70	0.9
> 2 pregnancies	11/70	9/70	0.8
Weeks of gestation	37.7 ± 1.78	37.95 ± 1.43	0.9

RESULTS

The study included 70 CD patients on GFD (group A) and 70 healthy controls (group B). According to the Oslo classification[1], CD patients were classified as classical CD in 31 cases (44%), non-classical CD in 34 subjects (49%), asymptomatic CD in 5 patients (7%). About symptoms of CD patients, 30 subjects (43%) showed anaemia, 31 (44%) had diarrhoea, 33 (47%) presented weight loss, 26 (37%) showed abdominal pain and 28 (40%) asthenia.

Group A and Group B resulted well matched for age (group A: 33.3 ± 2.9 years; group B: 32.3 ± 4.3 years; *P* = NS) and level of school education (group A: 11.1 ± 3.5; group B: 11.3 ± 3.9; *P* = NS).

No significant difference was evident between the two groups in terms of laboratory variables: haemoglobin (group A: 11.03 ± 2.46; group B: 11.21 ± 2.54; *P* = NS); cholesterol (group A: 156.85 ± 35.82; group B: 149.68 ± 37.02; *P* = NS); glycaemia (group A: 80.6 ± 10.3; group B: 79.81 ± 13.3; *P* = NS); alanine transaminase (group A: 25.41 ± 12.6; group B: 24.18 ± 11.9; *P* = NS). Demographic and serological features of patients and controls are reported in Table 1. The level of anti-transglutaminase antibodies was normal for all participants (CD patients on GFD and controls).

Thirty-three subjects in Group A and 10 in Group B had EPDS scores higher than the selected cut-off (47.1% of CD patients *vs* 14.3% of controls; $P < 0.01$; OR = 3.3). The Figure 1 shows the prevalence (%) of positive EPDS for PPD in CD women and controls. EPDS score was higher in CD women compared to the controls (mean score: group A 9.9 ± 5.9; group B 6.7 ± 3.7; $P < 0.01$). After psychiatric assessment, 29 out of the 33 patients in Group A (prevalence 41%) and 8 out of the 10 people in the control group (prevalence 11%) with high EPDS scores received a diagnosis of PPD. These results confirmed the high sensitivity of EPDS in our country

Table 2 Main results

	Group A Celiac women *n* = 70	Group B Healthy subjects *n* = 70	*P* value
EPDS score (mean ± SD)	9.94 ± 5.98	6.7 ± 3.73	< 0.01
Patients with EPDS score ⩾ 10 (%)	33/70 (47)	10/70 (14)	< 0.01
PPD after psychiatric assessment	29/33	8/10	0.06
SF-36			
PCS (mean ± SD)	55 ± 12	66 ± 8	0.03
MCS (mean ± SD)	43 ± 11	56 ± 7	0.02

EPDS: Edinburgh postnatal depression scale; PPD: Post-partum depression.

(sensitivity 86%). The majority of patients suffered from a mild form of PPD received only active psychological support; only 6 patients (16%) needed anti-depressants and long-term psychiatric follow-up. Results are reported in Table 2.

Regarding the circumstances of delivery, no significant differences were observed between the two groups in terms of type of delivery (group A: caesarean section delivery 51.4%; vaginal delivery 48.6%; group B: caesarean section delivery 44.3%; vaginal delivery 55.7%; P = NS) and birth outcomes (live birth: group A 100%; group B 100%; congenital malformations: group A 0%; group B 1.5%; P = NS). On the contrary, a significant association was observed between the onset of PPD and a previous menstrual disorder in women suffering from CD. Among these, 23 women with and only 7 without previous gynaecological diagnosis of menstrual disorders were positive for PPD at EPDS (69.7% *vs* 18.9%; $P < 0.001$; OR = 3.6); this association was not evident in the control group (25% *vs* 33%; $P = 0.4$).

With regard to quality of life as measured by the SF-36, outcomes were significantly better in controls than in patients with CD in terms of both PCS (55 ± 12 in Group A *vs* 66 ± 8 in Group B; $P = 0.03$) and MCS (43 ± 11 in Group A *vs* 56 ± 7 in Group B; $P = 0.02$). These outcomes were significantly and inversely correlated with the presence of PPD ($P = 0.02$).

DISCUSSION

The present study, focused on PPD, has shown a higher prevalence of this condition in women affected by CD on GFD when compared to healthy subjects (47% *vs* 14%); after psychiatric assessment, the prevalence of PPD was 41% in CD patients compared to 11% of control group. To our knowledge, this is the first paper reporting a higher incidence of this kind of psychiatric condition in CD.

Many studies have evaluated the psychiatric/mental aspects of CD[4,6,7]. In particular, a recent meta-analysis has clearly shown that depression is consistently more common and severe in adults with CD than in healthy adults[32]. After the diagnosis of CD, these patients must avoid foods containing grains (wheat, rye, and barley) for the rest of their life. From this point of view, depression in adult CD may represent a non-specific disorder precipitated by adverse physical symptoms along with personal and social limitations imposed by the chronic disease and the related dietary restrictions.

In effect, in terms of clinical depression, adults affected by CD do not differ substantially from those with other types of physical illness. In addition, many reports have underlined the high prevalence in patients with CD compared to healthy control groups of other psycho-pathological conditions, such as anxiety and sleep disorders[5,8,9].

In our study, a probable diagnosis of PPD identified on the basis of EPDS questionnaire scores was subsequently confirmed through psychiatric assessment in a majority of cases (sensitivity: 86%).

Although frequent, PPD was mild in most affected CD patients and was effectively treated by psychological support. This finding is in accordance with previous reports showing a high rate of missed diagnosis of PPD in the general population, especially if PPD presented in a mild form[33]. The screening approach led to early diagnosis and treatment in 43 women (33 CD, 10 controls) affected by PPD, potentially preventing negative consequences for mothers and their newborns.

The high prevalence of PPD in our CD population could be due to several causes. Firstly, PPD could be the expression of an underlying subclinical depression which develops features of PPD and clinical relevance during pregnancy or immediately after childbirth as a result of the heightened anxiety that can be typical of this period. This hypothesis is also in accordance with the low level of quality of life of CD patients compared to the controls[9,34]. On these bases, it is possible that a substantial proportion of the PPD cases were also mildly symptomatic during pregnancy so that the screening for and treating depression in CD patients during pregnancy might be more beneficial than waiting to screen them in the postnatal period. Many studies have highlighted the close relationship between low quality of life, anxiety and depression in patients with CD and, from this point of view, our findings are not surprising[4,9]. In addition, a woman suffering from CD may be concerned about the possible "genetic transmission" of CD to the newborn, thus worsening her anxiety.

Another explanation for our results could be found in inflammatory/autoimmune mechanisms. Many reports have investigated and underlined the possible role of inflammatory mediators in the pathogenesis of some variants of depression and of other mental problems such as sleep disorders[35,36]. Significant increase in pro-inflammatory cytokines and other inflammation-related proteins in major depression were found in plasma and cerebrospinal fluid. Furthermore, elevated levels of pro-inflammatory cytokines persist after clinical symptoms of depression are in remission and can also predict the onset of a depressive episode. Antidepressant treatment can lead to a normalization of elevated cytokine levels in major depression[35]. In effect, a recent meta-analysis has investigated the effect of some anti-depressants on the level of inflammatory cytokines. The results of this study

underlined that antidepressant treatment is able to reduce levels of IL-1β and possibly those of IL-6. Stratified subgroup analysis by class of antidepressant indicated that serotonin reuptake inhibitors may reduce levels of IL-6 and TNFα[36]. All these consideration could be considered an indirect demonstration of the pivotal role of inflammation in determining depression (and PPD) symptoms.

In our CD population the occurrence of PPD was significantly correlated with the presence of previous menstrual disorders[37]. This result could be the expression of a pre-existing underlying hormonal alteration which can also affect and/or contribute to the incidence of mental disorders[38,39].

Interestingly, a recent paper by Buttner *et al*[39] has highlighted the significant association between previous menstrual disorder and depression with a twofold increased risk of PPD in women with menstrual irregularities[40]. In our control population this kind of association was not evident, probably because of the small number of controls with PPD (10 patients). Nevertheless, one could postulate that this association may be related to the range of alterations characterising the spectrum of gynaecological/obstetric manifestations of CD[41,42]. Unfortunately, our work did not include investigations for the measurement of sexual and other hormones and this hypothesis remains therefore unanswered. On the other hand, no significant association was seen between PPD and type/outcome of delivery between the two groups of subjects. About this issue, our work confirmed once again the very high percentage of caesarean delivery performed in South of Italy[43,44].

Our work presents some limitations. First of all, we included all CD patients on GFD in our study; the full compliance to GFD was confirmed by the negative level of anti-transglutaminase antibodies in all CD patients. We decided to exclude patients with new/recent diagnosis of CD (who would be patients on free diet) because the majority of patients followed-up at our Centre consisted of individuals with previous diagnosis of CD and already on GFD. Hence, in order to recruit a homogenous population to the study, we decided to exclude patients who had recently been diagnosed with CD and were on free diet. However, thanks to the composition of our sample, we were able to document that PPD in patients suffering from CD is not directly related to active gluten ingestion. Further studies (ideally multicentre) are needed to define the prevalence of PPD in CD women on free diet (*e.g.*, diagnosed with CD during their pregnancy or immediately after childbirth).

We used healthy subjects as control group. This methodological approach is necessary to demonstrate the real increase of PPD in patients with CD compared to the general population; however, it does not determine whether the high prevalence of PPD is related to CD specifically or to a non-specific "illness status". In effect, as mentioned earlier[32], adults affected by CD do not differ substantially in terms of incidence of depression from those with other types of physical illness and the same could be true of PPD. In view of this, only a study directly comparing prevalence of PPD in patients with CD with that in patients suffering from other diseases (*e.g.*, inflammatory bowel diseases, rheumatologic diseases) could clarify this aspect.

However, the high prevalence of PPD in patients suffering from CD and the clinical relevance of this psychiatric condition justify the routine use of the EPDS questionnaire in women with CD who have recently given birth.

In conclusion, post-partum depression is a frequent condition in women affected by CD on GFD, particularly in those with history of menstrual disorders. We suggest screening for PPD in all women with CD for early detection and prompt treatment of this condition.

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COMMENTS

Background

Celiac disease (CD) is an autoimmune enteropathy gluten-related, characterized not only by gastrointestinal symptoms, but also by an increased prevalence of psychological symptoms and mental disorders, specially depression, anxiety and sleep disorders.

Research frontiers

Focused data on post-partum depression (PPD) in celiac women are still lacking.

Innovations and breakthroughs

In this case-control study, the authors evaluate, for the first time in the literature, the prevalence of PPD in CD patients on gluten-free diet compared to that of healthy subjects experiencing a recent delivery.

Applications

The authors demonstrated that PPD was present in 47.1% of CD women and in 14.3% of controls ($P < 0.01$; OR = 3.3). In the CD population the occurrence of PPD was significantly correlated with the presence of previous menstrual disorders. The authors suggest screening for PPD in all women with CD experiencing delivery for early detection and prompt treatment of this condition.

Terminology

PPD is a psychiatric disorder affecting women after pregnancy and leading to disruptions in maternal-infant interactions, and lower cognitive functioning and behavioural problems in children.

Peer review

In this manuscript, the authors present psychiatric disorders - showing higher incidence of PPD in patients with CD in comparison to healthy women controls. From the gastrological point of view this is a well written paper, but it should be evaluated by a psychiatrist to assess accuracy of psychological tests used for the assessment of depression.

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ORIGINAL ARTICLE

Retrospective Study

Hepatoma-derived growth factor expression as a prognostic marker in cervical cancer

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Abstract

AIM: To examine the association of hepatoma-derived growth factor (HDGF) expression with the prognosis of patients with cervical cancer of the uterus (CC).

METHODS: HDGF is a unique nuclear growth factor, and it may play an important role in the development and progression of carcinoma. HDGF expression in 88 CC patients aged 23 to 76 years (median, 54 years) was analyzed by immunohistochemistry. A rabbit polyclonal antibody against the C-terminal amino acids (aa 231-240) of the human HDGF sequence was used as primary antibody at a dilution of 1:5000. This specific anti-HDGF antibody was purified using C-terminal peptide-conjugated Sepharose columns. Staining of endothelial cells in the noncancerous areas of each specimen was used as an internal positive control. Samples with more than 80% of tumor cells showing positive immunoreactivity in both the nucleus and cytoplasm were regarded as HDGF index level 2, more than 80% positive immunoreactivity in either the nucleus or cytoplasm as level 1, and less than 80% in both the nucleus and cytoplasm as level 0. The chi-square test and Fisher's exact probability test were used to examine the relationship between HDGF expression and clinicopathologic parameters, and statistical significance was examined by the log-rank test. Multivariate analysis of factors related to survival was performed using Cox's proportional hazards regression model. Statistical significance was set at $P < 0.05$.

RESULTS: The five-year overall survival rate was 82.9%. Fourteen patients died due to tumors, nine of whom had tumor recurrence at 2-21 mo (median, 10 mo) after surgery. Tumor recurrence in five patients was determined at the time of the patients' deaths. Nineteen cases were regarded as HDGF index level 0, 11 as level 1, and 58 as level 2. Patients with level 2 expression showed higher rates of histological classification of keratinized squamous cell carcinoma

and adenosquamous carcinoma (44.8% of level 2 patients and 13.3% in levels 0 and 1), deep invasion (pT2-4 in 65.5% of level 2 patients, and 30.0% in levels 0 and 1), the presence of lymphatic invasion (50.0% in level 2, and 20.0% in levels 0 and 1), and the presence of lymph node metastasis (37.9% in level 2, and 6.7% in levels 0 and 1). Patients with an HDGF index of level 2 CC showed poorer 5-year overall survival rates than those with level 0 or 1 CC (74.0% and 100%, respectively, P = 0.0036). Univariate analysis revealed that histological classification (P = 0.04), depth of tumor invasion (P = 0.0001), vascular invasion (P = 0.004), and lymph node metastasis (P = 0.0001) were significant factors affecting overall survival in addition to HDGF expression. Multivariate analysis revealed HDGF expression level and lymph node metastasis as independent prognostic factors for overall survival (P = 0.0148 and P = 0.0197, respectively). The prognostic significance of HDGF was further analyzed in pT1 and pT2-4 patient groups, respectively. Among patients with pT1 CC, one the 39 analyzed patients died during the study, and no difference was observed among patients with HDGF index level 0, 1, or 2 CC. However, prognostic significance of the HDGF index was observed in the pT2-4 patient group, in which the mortality rates of patients with HDGF index level 2 CC and those with level 0 or 1 CC significantly differed (P = 0.0463).

CONCLUSION: The HDGF expression level is of prognostic significance in CC.

Key words: Hepatoma-derived growth factor; Prognosis; Cervical cancer; Immunohistochemical analysis; Multivariate analysis

Core tip: Hepatoma-derived growth factor (HDGF) is a unique nuclear growth factor, playing an important role in the development and progression of carcinomas. Prognostic importance of HDGF expression has been reported in several cancers. In the present study, HDGF expression in cervical cancer was examined by immunohistochemistry, showing increased HDGF expression as a marker of deep invasion, lymphatic invasion, and lymph node metastasis. In addition, HDGF expression was an independent prognostic factor for overall survival.

Song M, Tomoeda M, Jin YF, Kubo C, Yoshizawa H, Kitamura M, Nagata S, Ohta Y, Kamiura S, Nakamura H, Tomita Y. Hepatoma-derived growth factor expression as a prognostic marker in cervical cancer. *World J Obstet Gynecol* 2015; 4(1): 16-23 Available from: URL: http://www.wjgnet.com/2218-6220/full/v4/i1/16.htm DOI: http://dx.doi.org/10.5317/wjog.v4.i1.16

INTRODUCTION

Cervical cancer of the uterus (CC) is one of the most common carcinomas in females globally[1,2]. Human papilloma virus infection through sexual transmission is causative of CC carcinogenesis[3,4], and the rate of CC development in females of reproductive age is increasing worldwide[5,6]. More than 25% of patients with CC are under 40 years of age, and its occurrence in nulliparous women is increasing[7]. Due to the rise of mass screening, many cases of CC are detected at an early stage of the disease, and the number of curable patients is increasing[8]. Nevertheless, it is desirable to protect the fertility of nulliparous patients and patients of child-bearing age during treatment[5,6]. Thus, fertility-sparing surgeries, such as vaginal radical trachelectomy or abdominal radical trachelectomy, have been introduced[9,10].

Appropriate candidates for fertility-sparing surgery are patients with tumors classified by the International Federation of Gynecology and Obstetrics (FIGO) as stage IA1 with lymphovascular space involvement, IA2, and IB1 with tumors less than 2 cm in size[11]. In IB1 patients with tumors larger than 2 cm in size, higher risks of extrauterine spread and recurrence have been statistically demonstrated[12]. In cases in which lymph node metastasis is diagnosed or highly suspected, the surgery should be radicalized, or chemoradiotherapy should be undertaken instead[13].

Hepatoma-derived growth factor (HDGF) is a heparin-binding protein purified from the conditioned medium of the hepatocellular carcinoma (HCC) cell line HuH-7, which can proliferate autonomously in a serum-free chemically defined medium[14,15]. HDGF is an acidic 26 kDa protein consisting of 230 amino acids with no hydrophobic signal sequence in its N-terminus, and it has high affinity for the glycosaminoglycans heparin and heparan sulfate[16,17]. Exogenously supplied HDGF stimulates the proliferation of fibroblasts, endothelial cells, vascular smooth muscle cells, pulmonary epithelial cells and hepatocytes, as well as HCC, lung cancer and colon cancer cells, through the stimulation of ERK phosphorylation[18-20]. HDGF translocates to the nucleus, and this nuclear targeting stimulates cell proliferation[18].

Following these observations, we hypothesized that HDGF expression in human malignant tumors might influence metastasis and patient prognosis. Indeed, several reports have shown the correlation between increased HDGF expression and poor prognosis in cancers[21-24]. However, there have been no reports evaluating the correlation of HDGF expression with CC clinicopathologic features or prognosis.

In the present study, which included 88 patients with CC who were undergoing surgery, the expression levels of HDGF and the relationship between HDGF expression and clinicopathological features and prognosis were analyzed.

MATERIALS AND METHODS

Tissue specimens

Tumor tissue was collected from 88 patients with CC who underwent surgical resection between January 1995 and March 2002 at the Gynecology Department, Osaka Medical Center for Cancer and Cardiovascular Diseases,

Osaka, Japan. Patient ages ranged from 23 to 76 years (median, 54 years). Informed consent for the use of the specimens was obtained from all patients. The surgical procedures performed included cervical conization alone in two patients, total hysterectomy alone in five, total hysterectomy plus salpingo-oophorectomy in one, total hysterectomy plus salpingo-oophorectomy plus pelvic lymph node dissection in one, modified radical hysterectomy alone in three, modified radical hysterectomy plus salpingo-oophorectomy in two, modified radical hysterectomy plus pelvic lymph node dissection in one, modified radical hysterectomy plus salpingo-oophorectomy plus pelvic lymph node dissection in one, radical hysterectomy in six, radical hysterectomy plus salpingo-oophorectomy in 52, and radical hysterectomy plus salpingo-oophorectomy plus pelvic lymph node dissection in 14. Samples obtained from uterine lesions and dissected lymph nodes were fixed in 10% formalin and routinely processed for paraffin embedding. Histologic sections cut at a thickness of 4 μm were stained with hematoxylin and eosin, and immunoperoxidase procedures were performed [Avidin-Biotin Complex (ABC) method]. Histologic sections were reviewed by one of the authors (Tomita Y) to define the extent and mode of cancer invasion in the uterus as well as lymph node metastasis. Tumor stages were classified according to the FIGO and pTNM classification[25].

After surgery, all samples were examined by laboratory procedures, such as routine peripheral blood cell counts, and all patients underwent chest roentgenogram, computed tomography of the abdomen, colposcopic examination, and smear cytology at 6-12-mo intervals. Neoadjuvant chemotherapy was performed in nine patients. Adjuvant therapy was performed in 57 patients, radiotherapy alone in 26 patients, chemotherapy alone in 21, and combined chemo- and radiotherapy in nine. The chemotherapeutic protocols were as follows; fluorouracil (5-FU) or its derivative alone in six patients, cisplatinum (CDDP) or its derivative alone in 23, 5-FU and CDDP in one, and irinotecan in one. The follow-up period for survivors ranged from 12-145 (median, 88.2) mo. This study protocol was approved by the institutional review board of Osaka Medical Center for Cancer and Cardiovascular Diseases.

Immunohistochemical assays

Immunohistochemical studies were completed using the avidin-biotin-peroxidase complex method. Antigen retrieval was performed by heating the sections in 10 mmol/L citrate buffer (pH 6.0) for 5 min. A rabbit polyclonal antibody against the C-terminal amino acids (aa 231-240) of the human HDGF sequence was used as the primary antibody at a dilution of 1:5000. This specific anti-HDGF antibody was purified using C-terminal peptide-conjugated Sepharose columns[16,17]. Non-immunized rabbit IgG (Vector Labs; Burlingame, CA) was used as a substitute for the primary antibody to verify the possibility of false-positive responses due to the non-specific binding of IgG or the secondary antibody. Counterstaining was performed with hematoxylin.

Specimen classification based on immunohistochemical results

All immunohistochemically stained sections were blindly examined without any prior knowledge of the clinicopathologic parameters or patient outcome. Staining of endothelial cells in the noncancerous areas of each specimen was used as an internal positive control. Consistent HDGF expression in endothelial cells has been reported[19,20]. The HDGF expression pattern was independently evaluated in both the nucleus and cytoplasm; cells showing staining intensity similar to or stronger than that in the nucleus or cytoplasm of endothelial cells were regarded as nucleus positive or cytoplasm positive, respectively. Samples with more than 80% of tumor cells showing positive immunoreactivity in both the nucleus and cytoplasm were regarded as HDGF index level 2, more than 80% positive immunoreactivity in either the nucleus or cytoplasm as level 1, and less than 80% in both the nucleus and cytoplasm as level 0.

Statistical analysis

SAS software (Statistical Analysis System Institute, Cary, NC) was used for all statistical analyses. The chi-square test and Fisher's exact probability test were used to examine the relationship between HDGF expression and clinicopathologic parameters of prognosis. The cumulative survival rate was calculated by the Kaplan-Meier method, and statistical significance was examined by the log-rank test[26]. Multivariate analysis of factors related to survival was performed using Cox's proportional hazards regression model[27]. Statistical significance was set at $P < 0.05$.

RESULTS

Histologic findings

Histologically, 27 tumors were keratinizing squamous cell carcinoma, 60 were non-keratinizing squamous cell carcinoma, and one was adenosquamous carcinoma. Tumor cells invaded less than 5 mm (pT1a) in 14 patients, more than 5 mm but confined to the cervix (pT1b) in 27, beyond the uterus without parametrial invasion (pT2a) in 15, to the parametrium but not to the pelvic wall or lower third of the vagina (pT2b) in 28, to the pelvic wall or lower third of the vagina (pT3) in three, and to the mucosa of the bladder or rectum (pT4) in one. Sixty-four patients were node negative (pN0), and 24 had regional lymph node metastasis (pN1).

Patient outcome

The five-year overall survival rate was 82.9%. Fourteen patients died due to the tumors, nine of whom had tumor recurrence at 2-21 mo (median, 10 mo) after surgery. Tumor recurrence in five patients was determined at the time of the patients' deaths.

Expression of HDGF in CC

The HDGF staining pattern in CC varied; 65 cases (73.9%) showed strong staining in the nuclei of more than 80% of tumor cells and were thus regarded as nucleus positive, while 62 cases (70.5%) with strong cytoplasmic staining in

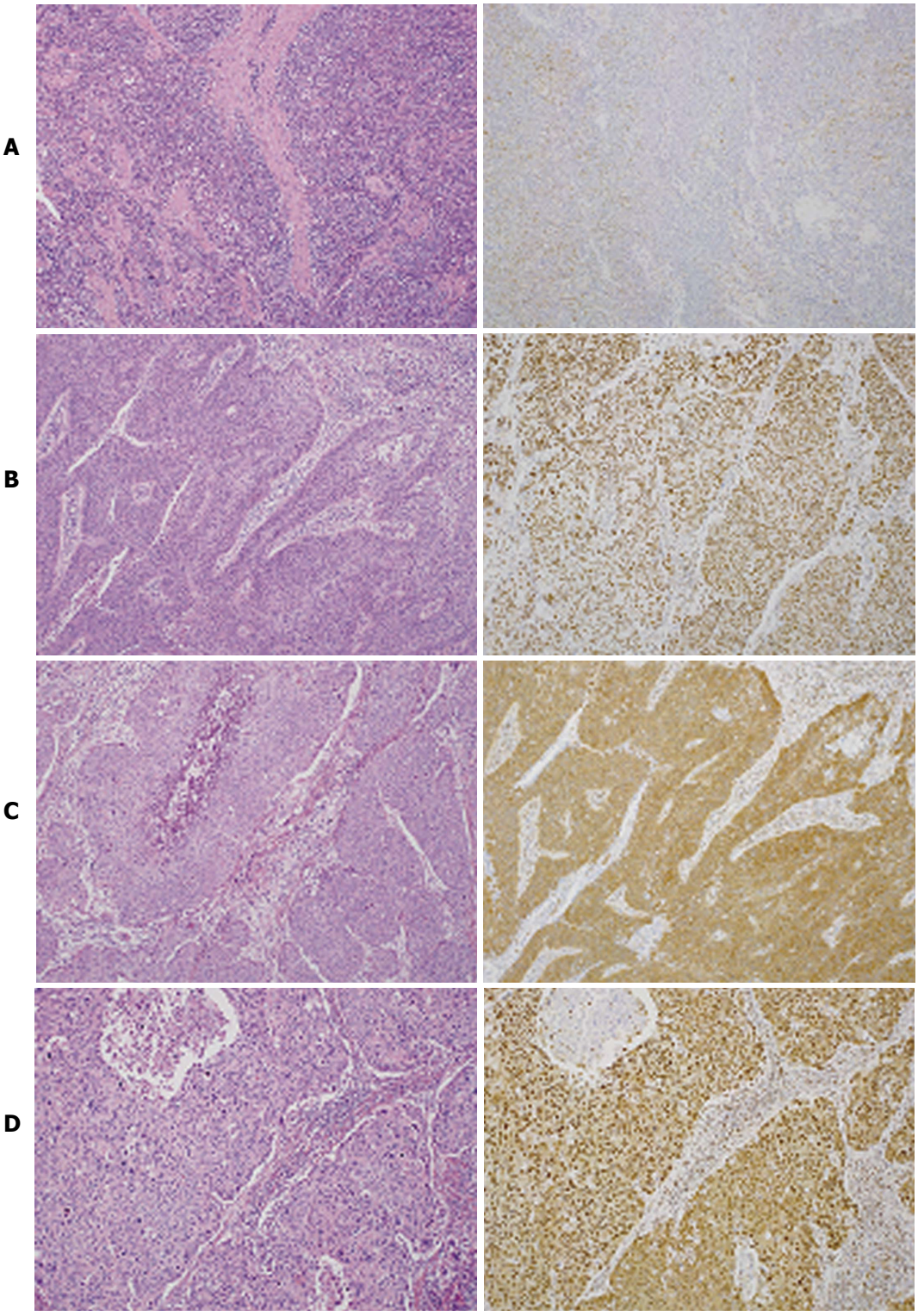

Figure 1 Hematoxylin and eosin staining (left lane) and hepatoma-derived growth factor immunohistochemistry (right lane). A: CC with HDGF index level 0. The majority of tumor cells were negatively stained for HDGF; B: CC with HDGF index level 1. More than 80% of tumor cells were positively stained in the nucleus, but negatively stained in the cytoplasm; C: CC with HDGF index level 1. More than 80% of tumor cells were positively stained in the cytoplasm, but negatively stained in the nucleus; D: CC with HDGF index level 2. More than 80% of tumor cells were positively stained in both the nucleus and cytoplasm (magnification × 50). CC: Cervical cancer of the uterus; HDGF: Hepatoma-derived growth factor.

more than 80% of tumor cells were cytoplasm positive. Fifty-eight cases (65.9%) determined as both nucleus and cytoplasm positive were regarded as HDGF index level 2. Eleven cases with HDGF expression either in the nucleus or the cytoplasm were classified as HDGF index level 1 and 19 others as HDGF index level 0 (Figure 1).

The relationship between clinicopathological features and HDGF expression in CC

The correlations between HDGF tumor expression

Table 1 Correlation of hepatoma-derived growth factor expression levels with clinicopathological factors in uterine cervical cancer patients *n* (%)

Factor	Category	No. of patients	HDGF expression			*P* value
			Level 0	Level 1	Level 2	
		n = 88	*n* = 19	*n* = 11	*n* = 58	
Age, yr		51.6 ± 13.8	46.7 ± 15.5	55.6 ± 12.1	52.4 ± 13.2	0.17
Histological differentiation	1: Keratinized SQ	29	2 (7)	2 (7)	25 (86)	0.037
	2: Nonkeratinized SQ	58	17 (29)	9 (16)	32 (55)	
	3: Adenosquamous carcinoma	1	0 (0)	0 (0)	1 (100)	
Lymphatic permeation	1: Absent	53	18 (34)	6 (11)	29 (55)	0.0006
	2: Present	35	1 (3)	5 (14)	29 (83)	
Vascular permeation	1: Absent	65	18 (28)	6 (9)	41 (63)	0.019
	2: Present	23	1 (4)	5 (22)	17 (74)	
Depth of invasion (pT)	1: T1	41	15 (37)	6 (15)	20 (49)	0.028
	2: T2	43	4 (9)	4 (9)	35 (81)	
	3: T3	3	0 (0)	1 (33)	2 (67)	
	4: T4	1	0 (0)	0 (0)	1 (100)	
Lymph node metastasis (pN)	1: Absent	64	12 (19)	9 (14)	36 (56)	0.0004
	2: Present	24	0 (0)	2 (8)	22 (92)	
Stage	1: Ⅰ	43	15 (35)	7 (16)	21 (49)	0.014
	2: Ⅱ	36	4 (11)	4 (11)	28 (88)	
	3: Ⅲ	5	0 (0)	0 (0)	5 (100)	
	4: Ⅳ	4	0 (0)	0 (0)	4 (100)	
Types of surgery	1: Conization	2	2 (100)	0 (0)	0 (0)	0.0001
	2: Total hysterectomy	7	7 (100)	0 (0)	0 (0)	
	3: Modified radical hysterectomy	7	4 (57)	0 (0)	3 (43)	
	4: Radical hysterectomy	72	6 (8)	11 (15)	55 (76)	
Salpingo-oophorectomy	1: Not performed	17	12 (71)	2 (12)	3 (18)	0.0001
	2: Performed	71	7 (10)	9 (13)	55 (77)	
Pelvic lymph node dissection	1: Not performed	71	14 (20)	9 (13)	48 (68)	0.7
	2: Performed	17	5 (29)	2 (12)	10 (59)	
Adjuvant/neoadjuvant chemotherapy	1: Not performed	53	16 (30)	5 (9)	32 (60)	0.03
	2: Performed	35	3 (9)	6 (17)	26 (74)	
Adjuvant radiotherapy	1: Not performed	52	16 (31)	9 (17)	27 (52)	0.003
	2: Performed	36	3 (8)	2 (6)	31 (86)	

SQ: Squamous cell carcinoma; HDGF: Hepatoma-derived growth factor.

and clinicopathological factors are shown in Table 1. In comparison to CC with HDGF index level 0 or 1, level 2 CC showed higher rates in the following categories: histological classification of keratinized squamous cell carcinoma and adenosquamous carcinoma (44.8% of level 2 patients and 13.3% in levels 0 and 1), deep invasion (pT2-4 in 65.5% of level 2 patients and 30.0% in levels 0 and 1), the presence of lymphatic invasion (50.0% in level 2 and 20.0% in levels 0 and 1), and the presence of lymph node metastasis (37.9% in level 2 and 6.7% in levels 0 and 1).

Uni- and multivariate analyses for the prognosis of patients with CC

Patients with HDGF index level 2 CC showed poorer 5-year overall survival rates than those with level 0 or 1 CC (74.0% *vs* 100%, $P = 0.0036$; Table 2, Figure 2A). In addition to HDGF expression, univariate analyses revealed that histological classification, depth of tumor invasion, vascular invasion, and lymph node metastasis were significant factors affecting overall survival (Table 2).

Multivariate analysis of factors significant in the univariate analyses revealed that HDGF index and lymph node metastasis were independent prognostic factors for overall survival (Table 3).

The prognostic significance of HDGF was further analyzed in pT1 and pT2-4 patient groups, respectively. Among patients with pT1 CC, one of the 39 analyzed patients died during the study, and no difference was observed among the groups. However, prognostic significance of the HDGF index was observed in the pT2-4 patient group, in which a significant difference in mortality was present between patients with HDGF index level 2 CC and those with level 0 or 1 CC (Figure 2B).

DISCUSSION

To identify optimal cutoff for the HDGF index in CC, statistical significance was examined at multiple cutoff levels, including < 50%, < 80%, < 90%, and < 100%. The prognostic significance was the greatest when the cutoff level was set at 80%. This categorization was therefore employed.

In the present study, CCs with HDGF index level 2 showed higher frequencies of deep tumor invasion (pT2-4), the presence of lymph node metastasis, and lymphatic invasion compared to level 1 and 2 cases, which are indicators of tumor progression in CC. In addition, patients with HDGF index level 2 CC showed a higher mortality rate compared with those with level 0 or 1. Previous studies have demonstrated that HDGF has a

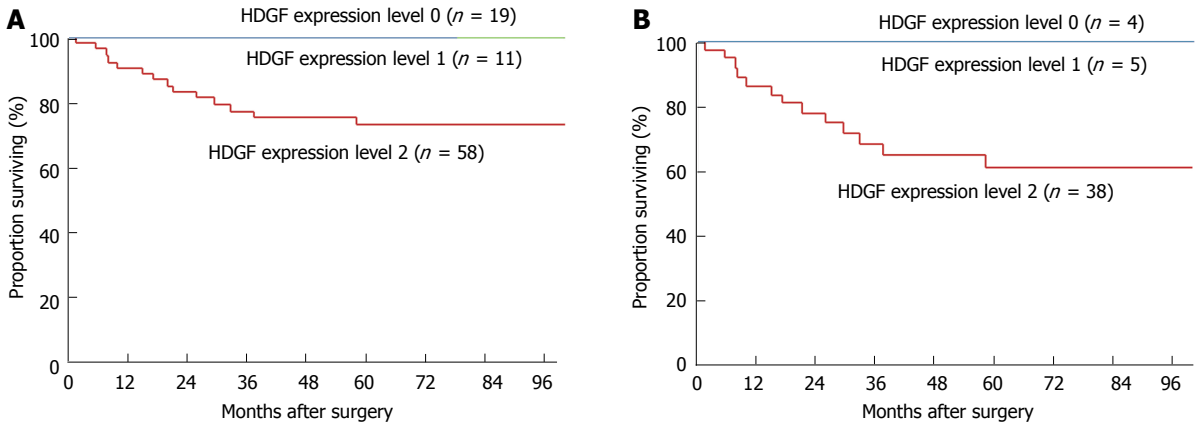

Figure 2 Overall survival curve of patients. A: Overall survival curve of patients with CC showing HDGF index levels 0, 1 and 2. Significant difference was observed between patients with HDGF index level 2 and other expression levels ($P < 0.0001$); B: Overall survival curve of patients with pT2-4 CC showing HDGF index levels 0, 1 and 2. Significant difference was observed between patients with HDGF index level 2 and other expression levels ($P = 0.0463$). CC: Cervical cancer of the uterus; HDGF: Hepatoma-derived growth factor.

Table 2 Univariate analysis of overall survival with clinicopathological factors in uterine cervical cancer patients

Factor	Category	No. of patients *n* = 88	No. of deaths *n* = 14	5-yr overall survival rate	*P* value
Age (yr)	1: ≤ 50	37	4	89%	0.27
	2: > 50	51	10	79%	
Histological differentiation	1: Keratinized SQ	29	5	81%	0.04[a]
	2: Nonkeratinized SQ	58	8	85%	
	3: Adenosquamous carcinoma	1	1	0%	
Lymphatic permeation	1: Absent	53	6	88%	0.15
	2: Present	35	8	75%	
Vascular permeation	1: Absent	65	6	90%	0.005
	2: Present	23	8	63%	
Depth of invasion (pT)	1: T1	41	1	97%	0.001[b]
	2: T2	43	10	75%	0.0001[d]
	3: T3	3	2	0%	
	4: T4	1	1	0%	
Lymph node metastasis (pN)	1: Absent	64	2	97%	0.0001
	2: Present	24	12	49%	
Stage	1: I	43	2	95%	0.0001[d]
	2: II	36	4	88%	
	3: III	5	4	20%	
	4: IV	4	4	0%	
Hepatoma-derived growth factor expression	1: Level 0	19	0	100%	0.0036[a]
	2: Level 1	11	0	100%	
	3: Level 2	58	14	74%	

[a]*P*: 1 and 2 *vs* 3; [b]*P*: 1 *vs* 2-4; [d]*P*: 1 and 2 *vs* 3 and 4. SQ: Squamous cell carcinoma.

Table 3 Multivariate analysis of overall survival with clinicopathological factors in uterine cervical cancer patients

Factor	Category	χ^2 value	*P* value
Histological differentiation	1: Keratinized and nonkeratinized squamous cell carcinoma 0: Adenosquamous carcinoma	0.51	0.474
Vascular permeation	1: Absent 0: Present	0.16	0.686
Depth of invasion (pT)-A	1: T1 0: T2-4	1.19	0.275
Depth of invasion (pT)-B	1: T1 and 2 0: T3 and 4	3.06	0.0801
Lymph node metastasis (pN)	1: Absent 0: Present	5.43	0.0197
Hepatoma-derived growth factor expression	1: Level 0 and 1 0: Level 2	5.94	0.0148

range of biological functions, including DNA synthesis, proliferation, growth stimulating activity, and vascular development[17-20]. The present study clearly indicates that HDGF is also involved in CC progression.

Fourteen of the 56 patients with HDGF level 2 expression died, whereas no deaths were observed among the 30 patients with HDGF level 0/1 expression. Although the distribution of patients was biased, the present results clearly indicate that HDGF expression is a useful marker to detect patients with CC who have a favorable prognosis. Indeed, multivariate analyses revealed the HDGF expression level to be an independent prognostic factor for CC. Analysis of the HDGF index together with other independent prognostic factors such as lymphatic invasion, vascular invasion, and lymph node metastasis might be a useful tool in predicting prognosis and determining appropriate therapeutic modalities for patients with CC.

Although patients with HDGF index level 0 or 1 can expect a favorable outcome after surgery, the occurrence of lymph node metastasis varied between the two groups. As patients with HDGF index level 0 CC showed no lymph node metastasis, they may suitable for fertility-sparing surgery. In contrast, patients with HDGF index level 1 or 2 exhibited a higher risk of lymph node metastasis; thus, standard surgeries such as radical hysterectomy are more preferable when the FIGO stage is higher than IA.

In conclusion, HDGF expression, as determined by immunohistochemistry, could be used as a new prognostic factor for CC. Although further study is still needed to elucidate the precise role of HDGF in CC malignancy, our results imply that HDGF may be a useful tool for determining the appropriate treatment of CC.

COMMENTS

Background

Cervical cancer of the uterus (CC) is one of the most common carcinomas in females, and its occurrence in nulliparous women is increasing. Fertility-sparing surgeries have been introduced to these patients, therefore assessment of histological grading of tumor is important. Expression of Hepatoma-derived growth factor (HDGF) in human malignant tumors might influence metastasis and patient prognosis, and reports have shown the correlation between increased HDGF expression and poor prognosis in several cancers, however, there have been no reports evaluating the correlation of HDGF expression and clinicopathologic features and prognosis of CC.

Research frontiers

HDGF expression as determined by immunohistochemistry could be used as a new prognostic factor for CC. Although further study is still needed to elucidate the precise role of HDGF in CC malignancy, the present report might imply that HDGF may be a useful tool in determining appropriate treatment of CC.

Innovations and breakthroughs

Fertility-sparing surgery, such as vaginal radical trachelectomy or abdominal radical trachelectomy, are introduced to patients with CC with the International Federation of Gynecology and Obstetrics (FIGO) stage IA1 with lymphovascular space involvement, IA2, and IB1 with tumors less than 2 cm in size. In cases where lymph node metastasis is diagnosed or highly suspected, the surgery should be radicalized, or chemoradiotherapy should be undertaken instead. The present study showed the correlation between HDGF expression and lymph node metastasis, then HDGF immunohistochemistry might be involved in the decisionmaking of CC treatment.

Applications

Patients with HDGF index level 0 CC showed no lymph node metastasis, they are suitable for fertility-sparing surgery. In contrast, patients with HDGF index level 1 or 2 have higher risk of lymph node metastasis; thus standard surgeries such as radical hysterectomy is more preferable when the FIGO stage is higher than IA.

Terminology

HDGF: a heparin-binding protein purified from the conditioned medium of the hepatocellular carcinoma (HCC) cell line HuH-7, which can proliferate autonomously in a serum-free chemically defined medium. HDGF is an acidic 26 kDa protein consisting of 230 amino acids with no hydrophobic signal sequence in its N-terminus, and it has high affinity for the glycosaminoglycans heparin and heparan sulfate. Exogenously supplied HDGF stimulates the proliferation of fibroblasts, endothelial cells, vascular smooth muscle cells, pulmonary epithelial cells and hepatocytes, as well as HCC, lung cancer and colon cancer cells, through the stimulation of extracellular signal-regulated kinase phosphorylation. HDGF translocates to the nucleus, and this nuclear targeting stimulates cell proliferation.

Peer review

The author gives information about the expression levels of HDGF in 88 patients with cervical cancer undergoing surgery, and the relationship between HDGF expression and clinicopathological features and prognosis. The research group has great experiences in this area.

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