

Cervical cancer – a real medical challenge when diagnosed during pregnancy

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ABSTRACT

One of the most common malignancies diagnosed during pregnancy is cervical cancer. If a local examination and a Pap-smear have not been done for screening, when some symptoms appear during pregnancy, they might be easily mistaken for pregnancy early related complaints. The treatment of cervical cancer during pregnancy should take into consideration many factors including the size of the tumor, lymph node involvement, gestational age, the wish of pregnancy continuation and fertility preservation. All these factors make the optimal treatment decision difficult to be taken and suggest that a multidisciplinary team including an obstetrician, neonatologist, medical oncologist, psychologist, pathologist, and radiologist, is necessary for the best management. This article reviews the existing studies, guidelines and recommendations regarding the diagnosis and management of cervical cancer during pregnancy.

Keywords: cervical cancer, pregnancy, pregnancy preservation, staging, neoadjuvant chemotherapy, gestational age

INTRODUCTION

Neoplastic diseases are one of the most important challenges in medicine nowadays. A situation that makes a cancer even harder to accept and to further treat it, is the one when it is diagnosed during pregnancy. Cervical cancer is the third most common gynecologic cancer. Even if there are methods of screening and prevention through vaccination, it remains a significant cause of morbidity and mortality in developing countries and sometimes, it is diagnosed only during pregnancy.

Even if cervical cancer incidence during pregnancy is generally low, between 0.05 and 0.1%, it represents one of the most common malignancies diagnosed during pregnancy, almost 75% of cases being diagnosed in the early stages. It seems that in the last time, a slightly increased incidence was observed, on the one hand because of the higher rates

of cancer in general and on the other hand due to the childbearing age, that was delayed up to the fourth decades of life [1-4].

Pregnancy complicated by cervical cancer represents a complex medical scenario from the initial diagnosis process to the therapeutic decision. Because studies on this topic are not plentiful, there are still many questions regarding the optimal management of this situation. This review article aimed to find in literature evidence-based information about diagnosis and management of cervical cancer during pregnancy.

MATERIALS AND METHODS

PubMed database was searched for studies published in the last 10 years, written in English, that analyzed cervical cancer during pregnancy regard-

ing method of diagnosis, staging and treatment. For the search in the PubMed database, combination of the following keywords was used: ‘cervical cancer’, ‘pregnancy’, ‘surgical management’, ‘pregnancy termination’, ‘chemotherapy’ or ‘imaging methods.

SIGNS AND SYMPTOMS

Similar to the non-pregnant women, clinical manifestations of cervical cancer differ depending on the stage. Moreover, during pregnancy or immediately postpartum, cervical cancer signs and symptoms may be mistaken for other diseases that could appear in this period, or might overlap with pregnancy related complaints. Most common manifestations are vaginal discharge (purulent or bloody), irregular vaginal bleeding, pelvic pain, flank pain or signs of anemia. However, in early stages, the neoplasia could be totally silent [1,5].

SCREENING AND DIAGNOSTIC METHODS

Screening and diagnosis of cervical cancer follows the same three steps as in a non-pregnant woman: cervical cytology, HPV-high risk genotyping, colposcopy, and cervical biopsy. However, what should be considered is that pregnancy bring up physiological changes that might lead to misinterpretations of the tests.

Cervical cytology

Studies have shown that Pap-smear is not associated with any risk of pregnancy loss or other complications [6]. Instead, a special attention should be given to the interpretation of the Pap-smear. Because maternal hormones levels lead to cellular alterations (glandular hyperplasia of cervical mucosa, irregular cell morphology, enlargement of nuclei, migration of squamous-columnar junction), a misdiagnosis of highly squamous intraepithelial lesions or even invasive cancer might be done, if the pathologist has not enough experience [4,7].

HPV-high risk screening will increase the accuracy of detection of precursor of cervical cancer and will offer the reason for colposcopy. The new guidelines of American Society for Colposcopy and Cervical Pathology (ASCCP) recommend performing colposcopy when HPV 16 and 18 are detected, even if cytology is negative [8].

Colposcopy

When abnormal cervical cytology is found, the second step to follow is colposcopy. Also, colposcopy evaluation during pregnancy is challenging because of the cervical appearance modifications. However, according to a recent study, the colposco-

py has a high specificity in pregnancy for the diagnosis of invasive carcinoma and is a reliable tool in the first two trimesters and especially in women ≤ 20 weeks pregnant. The reliability of colposcopy decreases after 20th week of gestation, being observed a higher risk of underestimation of the lesions [9].

Cervical biopsy

When high-grade cervical lesions or cervical cancer is suspected, cervical biopsy can be taken. It seems that, during pregnancy, cervical biopsy doesn't increase the rate of abortion or premature delivery, but on contrary, a curettage of cervical canal will do, which contraindicates this procedure [1].

STAGING

The staging of cervical cancer is the same during pregnancy as in non-pregnant women, according to International Federation of Gynecology and Obstetrics (FIGO) staging guidelines [10].

For assessing the local extension of the disease and the involvement of lymph node, the most used imaging procedure during pregnancy is magnetic resonance imaging (MRI). Because it uses no radiations, MRI is a safe procedure. Two studies have highlighted the role of MRI without contrast in cervical cancer staging during pregnancy, one conducted by Zanetta et al. on 6 patients [11] and another one, conducted by Balleyguier et al. on 12 patients [12], both of them proving a good sensitivity and specificity.

According to a recent study, PET-CT might also be taken into consideration for assessing cervical cancer staging in pregnant women. The study of Zanotti-Fregonara et al. included 6 pregnant women who underwent 18F-FDG scans as part of diagnostic workup for cancer and concluded that the total radiation exposure of the fetus and total absorbed dose from PET is below the threshold for harmful effect [13].

After the first trimester, when advanced disease is suspected, for assessing possible distant metastasis, chest X-ray might be safely performed, but shielding of the abdomen is highly recommended [2].

IMPORTANCE OF LYMPH NODE ASSESSMENT

One of the most important prognostic factors in cervical cancer is the lymph node status. Because MRI has a low specificity in lymph node assessment and because PET-CT is yet not routinely recommended, the laparoscopic surgery is the gold standard for lymph node assessment [14].

Staging lymphadenectomy could safely be done up to 22th week of gestation and should be performed for stage IA1 with lympho-vascular space invasion, for IA2 and IB1 stages. After the 22nd week of gestation, nodal resection is not anymore recommended because sufficient number of lymph nodes cannot be obtained. During pregnancy, sentinel lymph node biopsy is not an option because of the risk of anaphylactic shock when it is done with patent blue or because of the high-radiation dose when it is done with technetium [15].

Some physiological changes appear also into the lymph nodes during pregnancy and they could be mistaken as metastasis, when the histopathological evaluation is not done by an experienced pathologist [16].

Knowing the nodal status could have a major impact on management decision. When lymph nodes are positive, pregnant patient should be immediately informed and the treatment decision rapidly taken.

MANAGEMENT OF CERVICAL CANCER DURING PREGNANCY

There are four main factors to be considered in the management of cervical cancer in pregnancy: the stage, the fetal viability at the time of diagnosis, the wish of pregnancy preservation and the fertility conservation.

Pregnant patients with cervical cancer could be divided according to European Society of Gynecological Oncology (ESGO) into two groups depending on gestational age: less than 22-25 weeks and more than 22-25 weeks.

Management of cervical cancer at a gestational age less than 22-25 weeks

Conization

Conization of cervix without pregnancy termination could be a relatively safe treatment option for stage IA1 and for stage IA2-IB1 (tumor diameter less than 2 cm and when lymph nodes are not involved) [17]. However, there is a higher risk of premature birth when cervical conization is performed [18], that's why a preventive cervical cerclage is indicated in this situation [19].

Cervical resection

Even if, theoretically, in early stage IA2-IB1 cervical cancer (without lymph node involvement), radical abdominal or vaginal trachelectomy might be an option, there are few reasons why this procedure is not recommended during pregnancy. Among the explanations is the great risk of abortion before 22-25 weeks of gestation, the difficulty of the procedure and the important risk of severe hemorrhage [20]. Because simple trachelectomy is a less compli-

cated procedure, it can be used instead of radical trachelectomy for stages IA2-IB1 [21]. Cervical resection must be followed by a preventive cerclage.

Neoadjuvant chemotherapy

Starting from stage IB2 or higher stages, when the patient desires the continuation of pregnancy, neo-adjuvant chemotherapy (NACT) is the treatment of choice. This has the role to prevent cancer progression, allowing in the same time the fetal development. Currently, the recommended regimen for neoadjuvant chemotherapy is cisplatin with or without paclitaxel every three weeks [22,23].

Termination of pregnancy

The choice of pregnancy termination is possible usually until the 24th week of gestation (based on local legislation) and is recommended in advanced disease or even in early stages when the patient decides not to preserve her pregnancy.

In early stages, IA2-IB2, when the cancer is still operable, a radical hysterectomy can be performed. During the first trimester and early second trimester, the surgery could be performed with fetus in utero, but in the late second trimester, it could be performed after hysterotomy.

Starting with IB3 stage, when the option is chemoradiation, the way of pregnancy termination is also dependent on the gestational age. During the first trimester, starting chemoradiation with the fetus in utero will lead to fetus death within few days. This is not possible in second trimester as well, when hysterotomy is recommended as the first step. Also, taking into account ethical and psychological reasons, feticide could be taken into consideration before chemoradiation [24].

Management of cervical cancer at a gestational age more than 22-25 weeks

Postponing definitive treatment after delivery is an option for patients with stages IA-IB1.

In stages higher than IB1, when patients choose to continue their pregnancy, neoadjuvant chemotherapy is the treatment of choice, with the purpose of preventing disease progression [5]. After a gestational age of 35 weeks, chemotherapy is not recommended, taking into account that 3 weeks are necessary between the last cycle of chemotherapy and delivery in order to allow both maternal and fetal bone marrow to recover [25].

Timing and mode of delivery

Vaginal delivery is possible for patients with stages IA1 or IA2 cervical cancer [26]. From stage IB1 and higher, vaginal delivery should be avoided and cesarian section is indicated. The reasons why vaginal delivery should be avoided in advanced stages include the high risk of lymphatic spread, cervical laceration and episiotomy related metastasis [27]. Regarding the optimal delivery time, even if

it is preferred to be after 37 weeks of gestation, it will be decided depending on individual disease conditions [28].

Effects of neoadjuvant chemotherapy on the fetus

To what extent is the fetus affected by chemotherapy is not totally known, but it largely depends on the gestational age at the time of administration. When the gestational age is less than 15 weeks, possible adverse effects of chemotherapy include neurological abnormalities such as mental retardation and microencephaly, skeletal and genital malformations and growth retardation. Major abnormalities are rare between 15 and 25 weeks, and unlikely after 30 weeks [15].

The platinum-based chemotherapy is the NACT-advised regimen in pregnant women with cervical cancer, most of the time in combination with taxanes. Among platinum derivatives, cisplatin is considered less harmful in comparison with carboplatin. According to one systematic review and meta-analysis article, platinum derivatives are a safe choice of treatment during the second and third trimester of pregnancy, but they have a risk of abortion or congenital anomalies when used in the first trimester [29]. That's why NACT is not indicated in the first trimester [30]. Marnitz et al. realized the first study including 7 patients, regarding in vivo cisplatin concentration in the fetal-maternal compartment. The measurements showed that in umbilical cord blood and in amniotic fluid there are significantly lower levels of cisplatin in comparison to maternal blood and all patients delivered healthy babies [31]. Regarding the effects of taxanes on fetus, the information is even more limited. Some experimental studies on animals show only low levels of taxanes in fetal plasma and fetal tissues [32].

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Moreover, one systematic review realized by Zagouri et al. concluded that taxanes are a safe choice when administered during the 2nd and 3rd trimester [33].

CONCLUSIONS

Cervical cancer during pregnancy is a real challenge for both patient and doctor. In this clinical situation the psychological impact is very high and the patient needs specific counseling and psychological support. The screening and diagnosis of cervical cancer follows the well-known three-steps algorithm. Even if imaging methods are limited during pregnancy, they are very important for cancer staging. The most important factor for management decision is the gestational age at the time of diagnostic. Also, the lymph node status is a decisive factor for the treatment decision, and the patient should be informed what would be the best option of treatment in the situation when the nodes are positive. In very early stages, conization or simple trachelectomy could be appropriate management options, but in advanced stages when the patient desires pregnancy continuation, the treatment option remains neoadjuvant chemotherapy. However, starting neoadjuvant chemotherapy in the first trimester is generally not recommended. Termination of pregnancy might be the recommended option in advance stages when gestational age is less than 22-25 weeks, but the final decision will be taken by the patient in accordance with her wish of pregnancy preservation. Given that the number of cases of cervical cancer in pregnancy is not high, future studies are needed for improving management algorithm for this condition.

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