

REVIEW

MANAGEMENT OF CERVICAL CANCER DURING PREGNANCY– LITERATURE REVIEW

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ABSTRACT

Although the exact incidence of cervical cancer cases in pregnant women is not known, undoubtedly is the most common gynecological malignancy diagnosed during pregnancy. Association between the two entities does not seem to influence the oncological outcomes. However, the management of these cases remains a real challenge for the obstetrician and for the onco-gynecologist, fighting for two lives being necessary. Moreover, due to the rarity of cases, there are no standard guidelines, the therapeutic strategy being influenced only by small case series and observational studies. This is a literature review of the current therapeutic options available for the management of such cases.

Keywords: cervical cancer, pregnancy, management.

RÉSUMÉ

Approche du cancer du col utérin pendant la grossesse – revue de la littérature

Bien que l'incidence exacte des cas de cancer du col de l'utérus chez la femme enceinte ne soit pas connue, il s'agit sans aucun doute de la tumeur maligne gynécologique la plus courante diagnostiquée pendant la grossesse. L'association entre les deux entités ne semble pas influencer les résultats oncologiques. Cependant, la gestion de ces cas reste un véritable défi pour l'obstétricien et pour le gynéco-oncologue, se battre pour deux vies étant nécessaire. De plus, en raison de la rareté des cas, il n'existe pas de directives standard, la stratégie thérapeutique n'est influencée que par de petites séries de cas et des études observationnelles. Ceci est une revue de la littérature des options thérapeutiques actuelles disponibles pour la gestion de tels cas.

Mots-clés: cancer du col utérin, grossesse, management.

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INTRODUCTION

Association between malignant tumours and pregnancy represents an unfortunate eventuality in which a multidisciplinary team is needed in order to provide a good control of the oncological disease as well as a favourable evolution and maturation of the foetus^{1,7}. Although the overall incidence of malignant tumours has a peak around the fifth and sixth decades of age, postponing the decision of childbearing led to an increase of the number of cases developing malignancies during pregnancy^{8,9}. Moreover, certain gynaecological malignancies such as breast cancer might be more difficult to be established in pregnant women leading to a postponed diagnosis, in a more advanced stage of the disease¹⁰. Among gynaecological cancers diagnosed during pregnancy, the most commonly reported entities are represented by cervical and ovarian cancer¹.

THE DIAGNOSIS OF CERVICAL CANCER DURING PREGNANCY

Although the exact incidence of cervical cancer occurring during pregnancy is not known, is estimated that it occurs in one to 12 cases per 10,000 pregnancies. Moreover, although Papanicolaou test for cervical cancer screening is mandatory at the time of diagnosis of pregnancy, its interpretation might be difficult in certain cases in pregnant women¹¹. Whenever abnormal results of Pap tests are found, the investigative protocol should go further, being followed by colposcopy and biopsy of the suspect lesions^{1,12}.

MANAGEMENT OF NEOPLASTIC LESIONS OF UTERINE CERVIX DURING PREGNANCY

The presence of intraepithelial cervical neoplasia (CIN) in the absence of the elements of invasion does not force the clinician to perform any kind of therapeutic strategy until after birth. In such cases repeated colposcopies in each trimester of pregnancy and serial biopsies whenever progression is suspected represent the standard protocol¹. In cases presenting suspicion of micro-invasive areas conisation might be proposed; however, the method is associated with high rates of miscarriage, premature labour or bleeding, the rates of complications increasing if the procedure is performed at a later stage of the pregnancy. The decision of performing such manoeuvres should be performed in early pregnancy, after a discussion between the oncologist, obstetrician and oncogynecologist and the patient¹.

When it comes to the more advanced stages of the disease, the management of the oncological process takes into consideration the size of the tumour, the histopathological subtype, the lymph node status, the stage of pregnancy as well as the woman's wish according to the on-going pregnancy and to her obstetrical future¹. However, a standard therapeutic protocol for such cases is still missing^{1,11,13}.

In order to provide an adequate staging of the tumoral process, performing a MRI without contrast is mandatory; the technique is most efficient in order to provide an adequate characterization of both the tumour and the regional lymph nodes basins¹⁴. The results provided by the MRI studies should be completed whenever is possible by the ones provided by the ultrasound^{15,16}. As for the association of PET-CT, the method is contraindicated due to the high foetal uptake of radioactivity¹¹.

Whenever suspicion of lymph node metastases exists, lymph node biopsy should be performed in order to assess the stage of the disease. The procedure can be performed by laparoscopy between the 13th and the 22th weeks of pregnancy; however, the histopathological studies of the specimen should be carefully realised due to the fact that certain modifications induced by the pregnancy might be found at the lymphatic level (such as decidual) and can mimic the presence of micro-metastases especially in squamous cell lesions¹. In some cases, immunohistochemical studies might be needed, in order to orientate the diagnosis¹¹.

Stage IA

In patients in whom a stage IA cervical cancer is diagnosed, they might be advised for permanent observation during pregnancy; if the stage of the lesion does not advance, oncologic surgery might be postponed until after birth. If the lesion is detected during the first weeks of gestation, conization might be proposed¹.

Stage IB

In patients with stage IB cervical cancer, the status of lymph node stations is mandatory to be known; in cases with smaller than 2 cm lesions and negative pelvic lymph nodes, observation until after birth or simple trachelectomy during pregnancy are the options of choice^{1,11}. When it comes to larger than 2 cm lesions, it seems that simple trachelectomy in association with pelvic lymphadenectomy represent a viable therapeutic strategy¹⁷. In a recent study conducted by Salvo *et al.* and published in Gynaecologic Oncology Journal in 2018 the authors included 5 pregnant patients diagnosed with cervical cancer at a median gestational age of 12 weeks¹⁸. At the time

of diagnosis, the median diameter of the tumour was 27 mm while the median depth of invasion was 10 mm. In all cases simple trachelectomy followed by minimally invasive pelvic lymph node dissection was performed, the median number of retrieved lymph nodes being 14; however, a single patient presented micro-metastatic disease at the level of the lymph nodes. The procedure seemed to be efficient from both the obstetrical and oncological point of view: the patients delivered at a median gestational age of 39 weeks and, after a median follow-up of 75 months, there was no case of recurrent disease¹⁸.

Locally advanced stages

In cases diagnosed with locally advanced cervical cancer during pregnancy, the decision of performing chemo-irradiation is usually associated with abortion. In selected cases, neoadjuvant chemotherapy consisting of paclitaxel and carboplatin might be associated in the presence of the pregnancy; however, immediately after birth the therapeutic protocol should be completed with surgery and/or irradiation¹.

An interesting such case was reported by De Vincenzo *et al* in 2018¹⁹; the authors presented the case of a 35-year-old nulligravid patient diagnosed with a poorly differentiated squamous cell carcinoma during the 27th week of gestation. At that moment, the tumour was classified as a IB2 lesion, so the patient was treated with two cycles of paclitaxel and cisplatin; the treatment provided a partial response of the tumour so the patient was submitted in the 35th week of gestation to caesarean section in association with radical hysterectomy, bilateral salpingectomy, ovarian transposition, pelvic and para-aortic infra-mesenteric lymph node dissection. The histopathological studies excluded the presence of nodal or placental metastases; however, the patient was submitted to adjuvant external beam radiotherapy in association with chemo-sensitization with cisplatin. Postoperatively, although initially the new born presented no sign of disease, he developed at 22 months of age an acute myeloid leukaemia and necessitated bone marrow transplantation. The authors did not report any other complication in the new-born or mother's evolution¹⁹.

When it comes to the decision to terminate the pregnancy and submit the patient to the oncologic treatment sooner, it should be taken after a close analysis of each case in part. Moreover, the results reported so far in literature are rather conflicting, a standard therapeutic guideline not being available yet. While in the study conducted by Bigelow *et al.*²⁰ (in which the majority of cases were diagnosed with FIGO stage IB lesions) completing the pregnancy and giving birth after the 36th week did not influence the

overall oncologic outcome of the patients, Xia *et al* reported opposite results: in their study it seemed that patients who decided to delay the oncologic treatment in order to prioritise the pregnancy reported a poorer overall survival²¹. However, the Chinese study included more advanced stages of the disease, most cases presenting tumors larger than 4 cm and a more aggressive biological subtype²¹.

Vaginal delivery versus caesarean section in cervical cancer patients

When it comes to the type of delivery in cervical cancer patients, it seems that especially in cases presenting micro-invasive disease, caesarean section should be performed. In this way, it is estimated that the risk of local recurrence as well as the one of distant metastases decreases²¹⁻²³.

Moreover, in a recent consensus regarding the management of cervical cancer, when it came to the association of pregnancy, the authors stated that spontaneous delivery seems to negatively impact on the oncological outcomes and recommended performing a caesarean section (if possible after the 32nd week of gestation)²⁴.

Early and long-term outcomes of patients diagnosed with cervical cancer during pregnancy

As for the outcomes of these cases, it seems that the presence of the pregnancy does not influence significantly the early or long-term evolution^{20,25}. An interesting study regarding the management and outcomes of cervical cancer patients diagnosed during pregnancy was published by Bigelow *et al.* in the American Journal of Surgery in 2017²⁰. The study included 28 such patients diagnosed and treated between 1997 and 2013 at Brigham and Women's Hospital and Massachusetts General Hospital who were matched 1:2 with contemporaneous, non-pregnant women with cervical cancer diagnosed within the same period of time.

The cases were matched in terms of stage and age. There was no significant difference in terms of age, public insurance, race, parity, smoking habits or HIV infection association between the two groups; as for the stage of the disease, 56% of pregnant patients were diagnosed in FIGO stage IB1 of disease. When it comes to the moment of gestation when the diagnostic was established, on average patients were diagnosed in the 17th week of pregnancy, seven out of the 28 cases deciding for terminating the pregnancy when finding out the diagnostic. Moreover, all the seven cases were diagnosed in FIGO stage IB1 or higher. Among the remaining 21 cases who decided to continue the pregnancy, there was no important obstetrical complication, the mean gestational age

at delivery being 36.1 weeks while the mean birth weight was 2820 g; as for the Apgar score, its value was higher than 7 at 5 minutes for all new-borns. When it comes to the way of delivery, 10 cases had vaginal delivery, with no adverse event. As for the oncological outcomes, although pregnant patients reported a significant longer interval between the time of diagnosis and the moment of initiating the treatment when compared to not-pregnant counterparts (20.8 weeks versus 7.9 weeks, $p=0.0014$), there was no significant difference in terms of survival; moreover, none of the patients who died during the follow-up period did not delayed the treatment due to the pregnancy, all cases deciding for pregnancy termination or encountering a spontaneous abortion.

Among patients who decided to postpone the treatment until after birth, six cases were submitted to radical hysterectomy at the time of caesarean section while other eight cases were submitted to surgery at 6-8 weeks after delivery; however, patients who were submitted to simultaneous caesarean section and hysterectomy encountered a significantly higher amount of blood loss when compared to those submitted to interval radical surgery.

Among the 28 cases diagnosed with cervical cancer during pregnancy, three cases died during the follow-up period, all three cases deciding to have an abortion when hearing the diagnosis. The first case was finally diagnosed with a stage IVA cervical tumour, she was submitted to multiple cures of chemo-irradiation and died three years after initial diagnosis; the second case was diagnosed with stage IIB cervical cancer, was submitted to radio-chemotherapy, developed recurrent disease three years later and died five years after the initial diagnosis, while the third case was also diagnosed with stage IIB cervical cancer and underwent radio-chemotherapy. She also developed a recurrent disease one year later and died within 17 months. The study concluded that patients developing cervical cancer during pregnancy report similar outcomes with non-pregnant patients; however, a key factor is represented by the gestational age at diagnosis. As for the obstetrical outcomes, all women who continued the pregnancy delivered in the late preterm period without significant complication; the single parameter which was modified was the amount of blood loss, significantly higher in cases in which radical surgery was performed at the time of caesarean section²⁰.

CONCLUSIONS

Association between cervical cancer and pregnancy is a rare event and therefore, there is no standard therapeutic guideline in order to manage such

situations. The decision for both the oncological and obstetrical outcome should be taken by a multidisciplinary team consisting of oncologist, oncogynaecologist, and obstetrician and should be carefully discussed with the patient. In cases in which pregnancy preservation is possible, it seems that the preferred way of delivery remains the caesarean section.

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