REVIEW

MANAGEMENT OF CERVICAL CANCER DURING PREGNANCY– LITERATURE REVIEW

Alin BODOG¹, Nicolae BACALBASA²,3,4,*, Irina BALESCU ⁵, Mihaela VILCU³,⁴, Iulian BREZEAN³,⁴, Nicolae SUCIU³,⁶

¹ Oradea Medical University, Romania
² Center of Excellence in Translational Medicine, Fundeni Clinical Institute, Bucharest, Romania
³ „Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
⁴ „Ion Cantacuzino” Clinical Hospital, Bucharest, Romania
⁵ Ponderas Academic Hospital, Bucharest, Romania
⁶ National Institute for Mother and Child Health „Alessandrescu-Rusescu” Bucharest, Romania

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 gynécologue- 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.

Address for correspondence: Nicolae BACALBASA
„Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
Address: Dimitrie Racovita Street, No. 2, Bucharest, Romania
Email: nicolae_bacalbasa@yahoo.ro, phone 0040723540426
**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. 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. 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 disease. Among gynaecological cancers diagnosed during pregnancy, the most commonly reported entities are represented by cervical and ovarian cancer.

**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 Pap smear test for cervical cancer screening is mandatory at the time of diagnosis of pregnancy, its interpretation might be difficult in certain cases in pregnant women. Whenever abnormal results of Pap tests are found, the investigative protocol should go further, being followed by colposcopy and biopsy of the suspect lesions.

**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 protocol. 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 oncogynaecologist and the patient.

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 ongoing pregnancy and to her obstetrical future. However, a standard therapeutic protocol for such cases is still missing.

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 basins. The results provided by the MRI studies should be completed whenever is possible by the ones provided by the ultrasound. As for the association of PET-CT, the method is contraindicated due to the high foetal uptake of radioactivity.

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 22nd 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 decidua) and can mimic the presence of micro-metastases especially in squamous cell lesions. In some cases, immunohistochemical studies might be needed, in order to orientate the diagnosis.

**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 proposed.

**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. When it comes to larger than 2 cm lesions, it seems that simple trachelectomy in association with pelvic lymphadenectomy represent a viable therapeutic strategy. 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 weeks. 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 disease10.

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 case was reported by De Vincenzo et al in 201810; 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 an 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 (if possible after the 32nd week of gestation)24. 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 al20 (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 evolution20,25. 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 delay 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 che-motherapy 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 section.\(^{20}\)

**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.

**Acknowledgements:**

This work was supported by the project entitled „Multidisciplinary Consortium for Supporting the Research Skills in Diagnosing, Treating and Identifying Predictive Factors of Malignant Gynecologic Disorders“, project number PN-III-P1-1.2-PCCDI2017-0833.

**Compliance with Ethics Requirements:**

“The authors declare no conflict of interest regarding this article”

**References**

1. Skrzypczyk-Ostaszewicz A, Rubach M. Gynaecological cancers coexisting with pregnancy – a literature review. Contemp Oncol (Poln) 2016; 20 (3):193-198.
2. Davison J, Narain S, McEwan A. Cancer in pregnancy Obstetrics, Gynaecology And Reproductive Medicine 27:8; Elsevier 2017.
3. Azim HA Jr, Peccatori FA, Pavlidis N. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy Part I: Solid tumors. Cancer Treat Rev 2010; 36(2):101-109.
4. Peccatori FA, Azim HA Jr, Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 Suppl 6 vi160-vi170.
5. Khaled H, Al Lahloubi N, Rashad N. A review on thyroid cancer during pregnancy: Multitasking is required. J Adv Res 2016; 7(4):565-570.
6. Samarasinghe A, Shaf M. Cancer in pregnancy Obstetrics, Gynaecology And Reproductive Medicine 24:11 3 Elsevier 2014.
7. Genin AS, De Rycke, Y Stevens D, et al. Association with pregnancy increases the risk of local recurrence but does not impact overall survival in breast cancer: A case-control study of 87 cases. Breast 2016;30:222-227.
8. Kesic V. European survey on cancer and pregnancy: the ESGO data Cancer and Pregnancy symposium in Milan – Abstract Book Apr 2012.
9. Salani R, Billingssay C, Crafton SM. Cancer and pregnancy: an overview for obstetricians and gynecologists. Am J Obstet Gynecol 2014; 211 (1):7-14.
10. Parazzini F. Cancer and pregnancy, the burden of the problem. Cancer and Pregnancy symposium in Milan – Abstract Book Apr 2012.
11. Morice P, Uzan C, Gouy S, Verschraegen C, Haie-Meder C. Gynaecological cancers in pregnancy. Lancet 2012; 379(9815):558-569.
12. Ciavattini A, Serri M, Di Giuse J, et al. Reliability of colposcopy during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2018; 229:76-81.
13. La Russa M, Jeyarajah AR. Invasive cervical cancer in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2016; 33:44-57.
14. Balleyguier C, Fournet C, Ben Hassen W, et al. Management of cervical cancer detected during pregnancy: role of magnetic resonance imaging. *Clin Imaging* 2013; 37 (1):70-76.
15. Cibula D, Potter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients with Cervical Cancer. *Virchows Arch* 2018; 472 (6):919-936.
16. Epstein E, Testa A, Gauricikas A, et al. Early-stage cervical cancer: tumor delineation by magnetic resonance imaging and ultrasound – a European multicenter trial. *Gynecol Oncol* 2013;128 (3):449-453.
17. Favero G, Chiantera V, Oleszczuk A, et al. Invasive cervical cancer during pregnancy: laparoscopic nodal evaluation before oncologic treatment delay. *Gynecol Oncol* 2010; 118(2):123-127.
18. Salvo G, Frumovitz M, Pareja R, Lee J, Ramirez PT. Simple trachelectomy with pelvic lymphadenectomy as a viable treatment option in pregnant patients with stage IB1 (>2cm) cervical cancer: Bridging the gap to fetal viability. *Gynecol Oncol* 2018; 150 (1):50-55.
19. De Vincenzo R, Tortorella L, Ricci C, et al. Locally advanced cervical cancer complicating pregnancy: A case of competing risks from the Catholic University of the Sacred Heart in Rome. *Gynecol Oncol* 2018; 150 (3):398-405.
20. Bigelow CA, Horowitz NS, Goodman A, Growdon WB, Del Carmen M, Kaimal AJ. Management and outcome of cervical cancer diagnosed in pregnancy. *Am J Obstet Gynecol* 2017; 216 (3):276-276.
21. Xia T, Gao Y, Wu B, Yang Y. Clinical analysis of twenty cases of cervical cancer associated with pregnancy. *J Cancer Res Clin Oncol* 2015; 141 (9):1633-1637.
22. Hopkins, M P and Morley, G W The prognosis and management of cervical cancer associated with pregnancy *Obstet Gynecol* 1992;80(1):9-13.
23. Sood AK, Sorosky JJ, Mayr N, Anderson B, Buller RE, Niebyl J. Cervical cancer diagnosed shortly after pregnancy: prognostic variables and delivery routes. *Obstet Gynecol* 2000; 95 (6 Pt 1), 832-838.
24. Cibula D, Potter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. *Radiother Oncol* 2018; 127 (3), 404-416.
25. Hancheran A, Low J, Ng JS. Gynaecological cancer in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2012; 26 (3), 371-377.