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Review

High-grade cervical dysplasia in pregnancy – psychological and medical challenges

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Abstract

Despite being rare, the incidence of pregnancy-related cancer is expected to rise as women continue to delay childbearing and give birth later in their reproductive years. In this broad category, tumors like breast cancer, dermatological neoplasia and cervical cancer are most common and tend to arise in women of childbearing age. All pregnant women with clinical and cytologic suspicion of cervical cancer, except for squamous atypia or low-grade squamous intraepithelial lesions, should undergo colposcopy, with or without biopsy, the latter being avoided if possible due to possible complications which, although rare, may involve preterm labor initiation.

Some studies have attempted to assimilate comparable results of USG with MRI during the gestational period by determining the sensitivity, specificity, and accuracy of trans-rectal ultrasound (TRUS) in comparison to magnetic resonance imaging (MRI). In order to identify the proper way to diagnose and treat the disease, because of the complexity due to pregnancy, a multidisciplinary team consisting of a gynecologist, medical and surgical oncologist, and radiologist should be assembled. Both maternal and fetal wellbeing should be taken into consideration when the medical team must choose among termination of pregnancy, delay of maternal treatment, and iatrogenic preterm delivery. Psychological counseling also plays an important role and due to the sensitivity of the issue, should continue through gestation and the postpartum.

In order to develop optimal guidelines for diagnosis, treatment, and outcome issues, large scale prospective studies are needed, but feasibility may be limited due to the scarcity of cervical cancer cases associated with pregnancy.

Keywords: cervical cancer, pregnancy, psychological counselling

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Introduction

Although rare, the incidence of pregnancy-related cancer is expected to rise as women continue to delay childbearing and give birth later in their reproductive years (1). For a cancer to be categorized as pregnancy-associated neoplasia, it must be diagnosed during pregnancy or up to 1 year after delivery. The incidence rate for this type of cancer ranges from 17 to 38 cases/100.000 births (2-4).

Within this broad category, tumors like breast cancer, dermatological neoplasia and cervical cancer are most common and tend to arise in women of childbearing age. In fact, cervical cancer is the most frequently encountered gynecologic malignancy during the reproductive years (5), and its incidence has been steadily increasing over the past 2 decades (6).

Discussion

- *Pregnancy-related cervical cancer diagnosis and treatment; Clinical symptoms*

One major advantage is that due to the regular medical consultations associated with pregnancy, early detection is more likely (5). However, on the down side, while the pregnant woman has the same clinical symptoms of cervix carcinoma as the non-pregnant one, some of these symptoms, such as vaginal bleeding especially after sexual intercourse, may be misinterpreted and misdiagnosed as pregnancy-related rather than cancer-related issues. Others like pelvic pain, symptoms that mimic urinary and large bowel diseases, or sciatic-like pain can be mistaken for complications of pregnancy, leading to diagnostic delay for cancer.

- *Cytology*

Because of these circumstances, a high index of suspicion is required to diagnose carcinoma cervix during pregnancy, with screening programs focused on clinical symptoms, along with PAP smears, implemented in order to obtain an early stage diagnosis. All pregnant woman with clinical and cytologic suspicion of cervical cancer, except for squamous atypia or low-grade squamous intraepithelial lesions, should undergo colposcopy, with or without biopsy, the latter avoided when possible due to possible (though rare) complications such as preterm childbirth initiation. One of the clinical pitfalls that may occur because of physiological cervical changes during pregnancy such as increased vascularity, hypertrophy and hyperplasia of the endocervical glands, is that of a CIN-like (cervical dysplasia) diagnosis. Progression of low-grade dysplasia to carcinoma during pregnancy is rare (7).

A biopsy-confirmed LSIL is to be followed throughout pregnancy by cytologic examination each trimester and revaluated 8-12 weeks postpartum. For HSIL lesions, both cytologic and colposcopic monitoring is required every 8-12 weeks, especially because the regression rate in the postpartum period is very high. If diagnosed in the third trimester, fetal maturity is awaited, followed by delivery, and then appropriate oncologic treatment is administered.

A revised 2009 FIGO staging is used for the diagnosis and evaluation of cervix cancer in pregnancy.

- *Magnetic* resonance imaging (MRI)

MRI can highlight the lymph node status, tumor volume, and extent of the disease, with treatment decisions made accordingly. In early-stage cervical cancer, during the first and at the beginning of the second trimester, taking into consideration the importance of lymph nodes involvement, MRI as diagnostic tool (and a potentially laparoscopic lymphadenectomy as a means of treatment) provides a useful yet conservative approach. MRI provides important information for the management of cervical cancer during pregnancy, no matter which treatment is followed (8).

Gadolinium (a category C drug according to US Food and Drug Administration), despite having no

adverse affects to the neonate and being safe throughout the gestational period, should not be used unless absolutely necessary (9).

- *Ultrasound* vs. MRI

Some studies try to assimilate comparable results of USG (ultrasonography) with MRI during the gestational period by determining the sensitivity, specificity, and accuracy of trans-rectal ultrasound (TRUS) in comparison to magnetic resonance imaging (MRI), given the superiority of the latter in detecting incomplete resections after cervical conization (10). Results have demonstrated that TRUS is comparable to MRI in detecting the modification consistent with an early-stage cervical cancer. Other studies have also revealed that both TRUS and MRI are accurate and useful in preparation for treatment of women with early-stage cervical cancer, with the same result as above concerning ultrasound's accuracy in detecting residual tumors (11).

In conclusion, current evidence suggests that TRUS is appropriate for determining local invasiveness in cervical cancer, perhaps even more so than MRI. There is no evidence that Doppler ultrasound can give reliable information about tumor vascularization.

- *Computerized* tomography (CT-scan)

Sometimes the risk surrounding an improper diagnosis and in-time treatment are more important than the potential risk of imaging radiation. The International Committee on Radiological Protection (ICRP) recommends a max 100mGy dose; below that threshold no clinical studies have revealed an association with fetal death, deformity, or other developmental problems. Nevertheless, these examinations should be performed only when necessary and the dose should be as low as possible.

In order to standardize all external and internal dosages, a new generation of models is under development using standardized software for internal dose calculations based on the dose estimates for radio-pharmaceuticals (12).

- Positron emission *tomography* (PET-CT)

The fetal radiation dose from 18F-FDG PET studies is below the dose that can determine effects of radiation exposure to the fetus (13). Nevertheless, this procedure is more sensitive and specific than other imaging tools and can be applied as a staging and restaging method to guide treatment.

- *Additional* imaging tools

As additional imaging tools, cystoscopy and sigmoidoscopy are also safe during pregnancy, and can contribute to a differential diagnosis as well as the diagnosis of some of the complications due to local extension of cervix neoplasia.

- *Tumor* markers

Some tumor markers (including CA 125 and squamous cell carcinomaantigen SCC) can be elevated during normal pregnancy. In relation to SCC, serum levels are found in between 57% and 70% of women with a primary squamous cell carcinoma of the cervix, but also in different levels in patients with squamous cell carcinomas of the head and neck, esophagus, lung, and adenocarcinomas of the ovary and uterus. Therefore, SCC results must be corroborated with clinical and imagistic findings to increase specificity of the diagnosis. Because these tumor markers can exhibit fluctuation during pregnancy, their role in diagnostic and treatment decision factor should be used with care (14).

- *Treatment* during pregnancy

Because of the case complexity due to pregnancy, a multidisciplinary team consisting in gynecologist, medical and surgical oncologist, and radiologist should be assembled to identify the best way to diagnose and treat the disease. Both maternal and fetal wellbeing should be taken into consideration when the medical team has to choose between termination of pregnancy, delay of maternal treatment, or iatrogenic preterm

delivery (15, 16). A mix of medical and personal decisions will be involved, and may include such factors as: stage of the disease, lymphatic nodes status, histological type, gestational age, and the patient's choice to continue the pregnancy (17).

Despite the scarcity of clinical studies, due to the low rate of pregnancy-related cancer cases, some guidelines can be drawn. For example, for patients with early-stage disease diagnosed during the first 2 trimesters, with absence of nodal involvement, there is an increasing tendency toward conservatory treatment, taking into consideration that progression to invasive disease stage during pregnancy is very rare (18). Not so long ago, these patients would have been treated by pregnancy termination, followed by standard treatment, but today, the course of action for pre-invasive disease during pregnancy is observation. Consistent with the International Federation of Obstetrics and Gynecology (FIGO), staging of the disease and proper treatment can be differentiated.

Stage IA

In early invasive adenocarcinoma (IA1 and IA2) because of the excellent prognosis, conservative surgery may be appropriate, since parametrium involvement is low (19). Nevertheless, individualization of therapy based on pathology review, risk assessment, and patient preference is recommended

For stage 1A1, cervical conization is both the diagnostic method and the elective treatment (if there are negative margins present), and is usually performed between 14 and 20 weeks gestation (20). The alternative is to continue the pregnancy until childbirth, with standard oncological treatment delayed until 4-6 weeks after vaginal delivery, unless obstetric indication calls for caesarean section. Lymphadenectomy is not mandatory, a fact demonstrated by a study on 560 non-pregnant women with stage IA1 and IA2 disease, with only 1.5% positive pelvic lymph nodes (21). For stage 1A2 or with lymphatic invasion, treatment includes hysterectomy with lymphadenectomy.

Stage IB1 (tumor size ≤2 cm)

Vaginal radical trachelectomy (VRT) and abdominal radical trachelectomy (ART) are similar in oncologic outcomes at this stage of illness, and are now considered reliable surgical procedures. Preliminary clinical studies reveal that less radical procedures (deep cone and simple trachelectomy) could be comparable with the results of VRT and ART (22, 23), therefore reducing the risk for both mother and child. First radical trachelectomy, described by Dargent and recently confirmed by Ungar (24, 25), provides a possible approach for fertility preservation in the non-pregnant woman.

Stages IB1 (tumor size >2 cm and higher stages)

Despite the similarity in oncological outcomes of VRT and ART, the results for this stage are less than optimal.

Neoadjuvant chemotherapy (NACT)

NACT should be avoided during the first trimester as this is the highest risk period for interfering with fetal development and causing birth defects. Therefore, thorough medical counseling and a careful choice of treatment is critical before commencing therapy (26).

NACT is an option to keep the progression of the disease low, until fetal maturation, and should be followed by radical hysterectomy postpartum. Even with indications that NACT can improve oncological outcome, only a few clinical studies support this approach and it remains unclear if it offers a benefit over surgery alone (27), considering that the physiological changes of pregnancy result in a decreased blood concentration of chemotherapeutic agents. Alternatively, postpartum cisplatin chemo-sensibilisation (after radical hysterectomy following cesarean and pelvic radiation) seems to be the path in the future (28).

Nevertheless, NACT for the treatment of locally invasive cervical cancer during the 2nd and 3rd trimester of pregnancy, partially due to the fetal protection offered by the placental barrier-function, appears be a good option until fetal viability is obtained and a standard oncological treatment can be implement (29). In the end, chemotherapy has only one major contraindication, namely, breastfeeding.

No matter which treatment path is chosen, thromboembolism prevention is critical as both cancer and pregnancy are risk factors.

- *How* and when should we deliver or terminate the pregnancy?

Vaginal birth has several advantages: less blood loss and fewer risks than operative delivery, shorter hospital stays, and more importantly, faster recovery in order to begin chemotherapy. Disadvantages may include trauma of the lower uterine section and possible wound metastasis. In contrast, if pregnancy is to be terminated, the best timing should balance the risks and benefits for the mother and fetus. In situations involving life-threatening maternal disease, priority is given to maternal health management. Nevertheless, cancer treatment during pregnancy includes risks for the fetus. Terminating the pregnancy earlier in order to enable standard oncological treatment includes risks as pregnancy loss or preterm childbirth.

Neonatal outcome

Despite the fact that most studies have revealed good results for the fetus on long term follow up, neonatal outcome depends upon the type of treatment and more importantly, the age of gestation when the patient undergoes treatment. Complications after treatment are: pregnancy progression arrested, low or mediocre Apgar score, and perinatal mortality. Nonetheless, there is always a high risk of prematurity (especially after chemotherapy), with major negative outcomes: fetal morbidity and mortality.

- *Psychological* aspects

During pregnancy, psychological resilience is elevated due to the fact that the mother is “fighting” for her child. After childbirth, it is often more difficult for the woman to deal with cancer diagnosis and treatment. The combination of postpartum depressed mood to different degrees and sleep deprivation makes these patients extremely vulnerable. Thus it is important to discuss these issues with the patient before delivery and continue with psychological treatment after.

Counseling plays an important role and, due to the sensitivity of the issue, all options should be discussed with both mother and spouse/partner/father. .Extensive counseling regarding risks could improve both short and long term psychological outcomes (30).

Conclusions

Because of the complexity surrounding pregnancy, a multidisciplinary team that includes gynecologist, medical and surgical oncologist and radiologist is required to establish the best way to diagnose and treat the disease. Both maternal and the fetal well-being should be considered when the medical team must choose between termination of pregnancy, delay of maternal treatment, or iatrogenic preterm delivery. Psychological counseling plays an important role and due to the sensitivity of the issue, should continue through gestation and the postpartum.

In order to develop optimal guidelines for the diagnosis, treatment, and treatment efficacy, large prospective studies will be required, although due to the low prevalence of cervical cancer cases associated with pregnancy, carrying out such studies will present a challenge.

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