Best Practice & Research Clinical Obstetrics and Gynaecology 33 (2016) 102–107

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

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Neoadjuvant chemotherapy in cervical cancer in pregnancy

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Keywords:
cervical cancer in pregnancy
neoadjuvant chemotherapy
fertility preservation

Cervical cancer is the most common gynecological cancer encountered in pregnancy. The standard treatment of early cervical cancer is usually surgical removal of the cervix (in selected cases) or, more commonly, the uterus. However, when cervical cancer develops during pregnancy, definitive surgical treatment often needs to be postponed until the fetus reaches maturity. Neoadjuvant chemotherapy (NACT) is an innovative approach in the management of these patients. It helps in controlling the disease and delaying delivery. The paper presents a literature review of the history of NACT, as well as practice points and agenda for further research.

Introduction

The standard of care in the treatment of cervical cancer is surgery in early stages and chemoradiation in the more advanced stages. Surgery may involve only the removal of the cervix, in cases where fertility preservation is important, or a hysterectomy when this is not considered. With chemoradiation, fertility preservation is not possible currently.

When cervical cancer is diagnosed in pregnancy, it presents a complex situation for the patient and her physician. It necessitates a multidisciplinary approach involving the gynecologic oncologist, radiation oncologist, medical oncologist, obstetrician, pathologist, and, most importantly, the patient.

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http://dx.doi.org/10.1016/j.bpobgyn.2015.10.008
1521-6934/

Her concerns for the health of the unborn fetus, herself, and future fertility will all have a great impact on the final mode of treatment. The same considerations present a very difficult situation for the treating physician. Among these, the most difficult is the need for fertility preservation. Fertility preservation is usually considered only in early-stage (stages 1 and 2A) cervical cancer in pregnancy.

NACT is an innovative way of managing cervical cancer in pregnancy. It helps in controlling the disease and delaying delivery in patients whose fetuses have not reached the state of viability. It may also help reduce tumor size and thus enable performing fertility-sparing procedures such as trachelectomy. This review highlights the types of drugs used in NACT and their effects on the fetus and the mother, and the efficacy of NACT in treating cervical cancer in pregnancy by reviewing the published literature.

Chemotherapy in pregnancy

Chemotherapy has been used in pregnancy since the early 1950s [1]. The first clinical experience with chemotherapy during pregnancy was reported by Aviles et al. in 1988 [2]. They treated women with hematological malignancies during pregnancy where any delay in treatment would have been fatal to the mother and child. The most detrimental consequences of using chemotherapeutic agents include their potential teratogenic effects and the risk of miscarriage. The teratogenicity of any drug depends on the timing of exposure, the dose, and the degree to which the drug crosses the placenta. The most vulnerable period appears to be the period of organogenesis, weeks 2–8 after conception [3]. First-trimester use of chemotherapy may result in spontaneous abortion, fetal death, and fetal malformations. When the drugs are administered in the second and third trimester, there is an increased risk of intrauterine growth restriction and low birth weight. However, long-term studies have shown no significant effect on learning disabilities or any hematological or immunological abnormalities. In a prospective study of 70 children who were exposed to chemotherapy in utero, the general health, cognitive development, and cardiac outcome levels were comparable to those of the general population (median follow-up: 22 months) [4]. Conversely, it is well known that prematurity is associated with impaired cognitive function and it should be avoided whenever possible. The decision to use chemotherapy during pregnancy must balance the risk to the fetus versus prolonging maternal survival.

Many different types of chemotherapeutic agents have been used in pregnancy, depending on the malignancy being treated. In this article, we will confine ourselves to the agents that have been used to treat cervical cancer in pregnancy. These primarily include cisplatin, vincristine, and bleomycin. More recently, there have been reports of the use of carboplatin and paclitaxel in these patients. Among these, cisplatin is the most widely used drug. The side effects of cisplatin in nonpregnant patients are well documented, but its effects on the fetus have not been well studied. Most reports on the use of cisplatin in pregnancy are either small, retrospective studies or individual case reports. The pharmacokinetics of drugs in pregnancy is not very well understood. The physiological changes occurring during pregnancy affect drug absorption, distribution, and metabolism. These alterations are more pronounced during the third trimester of pregnancy, which may alter the efficacy and toxicity of the chemotherapeutic agents [5]. Knowledge about the transplacental passage of chemotherapeutic agents in humans is very limited. Besides, the metabolism of platinum in pregnant patients may be different from that in the nonpregnant women. In the first study of its kind, Marnitz et al. [6] measured cisplatin concentrations in seven patients presenting with cervical cancer in pregnancy. Synchronous samples of maternal blood, umbilical cord blood, and amniotic fluid were collected. All patients had delivered healthy babies. The cisplatin concentrations in the umbilical cord and amniotic fluid were 31–65% and 13–42% of the maternal blood, respectively. The authors concluded that there was a significantly lower level of cisplatin in the umbilical cord blood and amniotic fluid compared to maternal blood and that these findings ensure additional safety in using neoadjuvant cisplatin chemotherapy in pregnancy. However, they emphasized that a long-term oncologic and pediatric follow-up is essential to confirm the safety of this practice. In animal studies, it has been found that <2% of the maternal plasma levels of taxanes are found in the fetal plasma; in the case of carboplatin, fetal plasma concentrations reach up to 60% of the maternal levels [7].