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SPECIAL ARTICLE

Adjuvant Chemotherapy for Malignant Ovarian Germ Cell Tumors in Pregnancy

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ABSTRACT

Malignant ovarian germ cell tumors (MOGCTs) are uncommon in pregnancy, and therefore few gynecologic oncologists obtain expertise in this area. Management of MOGCTs in pregnancy is complicated and complex, requiring a multidisciplinary team in a specialized center. Fertility-sparing surgery is the first choice treatment of MOGCTs, while adjuvant chemotherapy is reserved for high risk cases. The indications for adjuvant chemotherapy after surgery are similar to those for non-pregnant women. Due to the low incidence and insufficient published data, the decision concerning adjuvant chemotherapy is based on case reports or small retrospective cohort studies. Following is a brief review of current knowledge concerning the MOGCTs in pregnancy and its management, especially, adjuvant chemotherapy.

Keywords: malignant ovarian germ cell tumor, ovarian cancer, pregnancy, management, chemotherapy.

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Introduction

Malignant ovarian germ cell tumors (MOGCTs) are infrequent form of ovarian tumors, arising from germ cells of the embryonic gonad. These tumors often grow rapidly, causing acute abdominopelvic pain that lead to early detection and treatment, thus these tumors are most often diagnosed in their early stages. They also usually occur in young women and are often unilateral. Nowadays, fertility-sparing surgery is the cornerstone primary treatment for MOGCTs, while adjuvant chemotherapy is kept for selected or high risk cases (generally indicated in all cases except for stage IA dysgerminoma or grade 1 immature teratoma)[1].

The incidence of MOGCTs in pregnancy is estimated at 1 in 12,500-25,000 pregnancies[2].

With the increasing use of routine ultrasonographic screening in pregnant women, it is forecast that more pregnant women will be diagnosed with ovarian cancer, especially MOGCTs, in the future.

When management of MOGCTs in pregnancy is considered, the gynecologic oncologist needs to carefully balance fetal (fetal loss, treatment-related complications to the fetus), maternal (potential loss of the reproductive function after cancer treatment, anxiety) and malignancy (oncological outcomes) concerns[3]. The management of MOGCTs in pregnancy, especially the decision whether or not to include adjuvant chemotherapy, is complicated. Due to insufficient data and the lack of randomized clinical studies, the decisions concerning adjuvant chemotherapy are based on a small number of case reports or small retrospective cohort studies[4]. Herein following is a short survey of current knowledge on adjuvant chemotherapy for MOGCTs in pregnancy (including data on safety outcomes for mother and fetus).

Clinical / pathological profiles

In a systematic review covering 102 MOGCTs in pregnancy, the two most common histological types were dysgerminoma and endodermal sinus tumor (EST)[3]. The median age of these women was 25.8 years, and 35.3% had abdominal/pelvic pain, 19.6% had abdominal distension, and 19% had growing mass. Accidental tumor discovery, such as during routine ultrasound, was reported in 21.6% of the cases[3].

Treatment during pregnancy

Fertility-sparing surgery with full peritoneal staging (peritoneal biopsy, omentectomy or omental biopsy, and peritoneal washing) should be done, but routine pelvic and para-aortic lymphadenectomy during surgery are not indicated[5, 6], although suspicious palpable lymph nodes should be removed. The indications for adjuvant chemotherapy after surgery are similar to those in non-pregnant women[6, 7].

Adjuvant Chemotherapy

Maternal physiological changes and stage of fetal development (the all-or-none period, organogenesis, and fetal phase) are the two most important factors when considering chemotherapy in pregnant women[8-10].

Several physiologic changes during pregnancy such as alterations in blood volume, albumin levels, hepatic metabolism and renal elimination may affect the pharmacokinetics of chemotherapeutic drugs, and consequently it is difficult to decide the optimal dose of chemotherapy that will actually be transported to the tumor site, perhaps leading to reduced drug effectiveness[9-11]. However, there is no evidence at present that dose adjustments are necessary to improve efficacy[10], and the current guideline recommends dosing chemotherapeutic drugs in pregnancy according to the women's weight[9].

The first trimester is the period of organogenesis of the fetus, and chemotherapy is contraindicated during this trimester to avoid interference with organogenesis, as early chemotherapy treatment has been correlated with a 10% to 20% risk of malformation[8, 9, 12, 13]. The risk of malformation drops to 1.3% in the third trimester[13]. From several previous studies and reviews, it appears that administration of some chemotherapeutic agents (such as bleomycin, platinum agents, anthracyclines, and taxanes) after the first trimester is relatively safe. However, there are also relatively higher risks of premature rupture of membranes, preterm labor, low birth weight, intrauterine growth restriction, and still birth[3, 8, 9, 11, 13-15]. Thus, in general the fetal benefits of delaying chemotherapy treatment until the second trimester counterbalance the increased maternal risks[9].

Chemotherapy should be avoided after 35 weeks of gestation or stopped 3 weeks before the expected date of delivery to allow recovery from possible bone marrow suppression of both mother and newborn, and to reduce the maternal risk of bleeding and infection[8-10].

Chemotherapy drugs and combination regimens

In pregnant women with MOGCTs, the indications for adjuvant chemotherapy after surgery are mostly similar to those in non-pregnant women with MOGCTs[4, 7]. From the 1990s until now, the combination of bleomycin, etoposide and cisplatin (BEP) has been considered the first line or standard regimen for adjuvant chemotherapy for non-pregnant women with MOGCTs[1]. For MOGCTs during pregnancy. There are conflicting datas in using BEP as a first line standard of treatment[7].

In 1999, Elit et al. reported a case of neonatal complications after BEP treatment of an EST during pregnancy. The neonate was born with significant ventriculomegaly with cerebral atrophy after 1 cycle of BEP during the third trimester[16]. In another case, a neonate suffered hearing impairment after being exposed to BEP treatment in utero[4, 17]. Based on this poor neonatal outcome and given the paclitaxel activity in MOGCTs[4,18], paclitaxel and carboplatin (PC) is becoming a point of interest[15]. In 2007, Hubalek et al., reported the first case of dygerminoma in a pregnant woman treated with PC during the third trimester with good response, and no adverse effects on the fetus[15]. Vinca alkaloids (especially vinblastin) has been in use for a long period of time, and the oncological outcome of patients with stage I MOGCTs treated with bleomycin, vinblastin and cisplatin (BVP) is nearly similar to that of those treated with BEP[3, 4, 19]. In addition, many case reports have found their use relatively safe in pregnancy[3, 4, 20, 21]. Based on the possible fetal risk and the high risk of secondary leukemia after etoposide treatment, two international consensus meetings (3rd of July 2008 and 17th of May 2013, both in Leuven, Belgium) suggested that PC or BVP should be considered in pregnant women with MOGCTs[4, 22].

Also, since 2000, several studies, including a systematic review of the literature, have reported that etoposide use during pregnancy (after the first trimester) in combination with cisplatin with or without bleomycin appeared to be safe[3, 23-26]. Consequently, in 2019, a third international consensus meeting suggested that BEP or etoposide with cisplatin (EP) should be preferred as adjuvant chemotherapy for pregnant women with MOGCTs[9].

Conclusion

MOGCTs during pregnancy are rare. Management of this cancer is an especially difficult issue as both the mother and fetus may be influenced. Unfortunately, decision concerning the optimal therapeutic management including adjuvant chemotherapy for this cancer is mainly based on case reports and small retrospective studies. In addition, data regarding long term outcomes of individuals exposed to adjuvant chemotherapy during pregnancy are limited. Thus, therapeutic decisions and treatment should be undertaken in specialized centers, and with personalized counselling.

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