

Early pregnancy following multidrug regimen chemotherapy in a gestational trophoblastic neoplasia patient

A case report

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Abstract

Rationale: Gestational trophoblastic neoplasia is a group of rare tumors that can be cured using chemotherapy. The use of artificial contraception for at least 1 year is recommended not only due to the high recurrence rate in the first year after treatment, but also because of the unclear genetic toxic effects of multidrug regimen chemotherapy on reproductive cells. There is no consensus about the contraception duration, but most patients want to have children.

Patient concerns: This case involved a 33-year-old female suffering from gestational trophoblastic neoplasia and 5-fluorouracil + actinomycin-D chemotherapy. She became pregnant 1 month after finishing the chemotherapy.

Diagnosis: Gestational trophoblastic neoplasia.

Interventions: No treatment during pregnancy.

Outcomes: The patient had a full-term normal delivery, and the baby showed normal development and growth after a follow-up of 48 months.

Lessons: Pregnancy soon after chemotherapy can be viable with rigorous prenatal care.

Abbreviations: 5-Fu = 5-fluorouracil, Act-D = actinomycin-D, CT = computed tomography, DNA = deoxyribonucleic acid, FIGO = International Federation of Gynecology and Obstetrics, GTN = gestational trophoblastic neoplasia, hCG = human chorionic gonadotropin, LMP = last menstrual period, MTX = methotrexate, NT = nuchal translucency, QD = quaque die, RNA = ribonucleic acid.

Keywords: 5-fluorouracil, actinomycin-D, chemotherapy, gestation, gestational trophoblastic neoplasia

1. Introduction

Gestational trophoblastic neoplasia (GTN) is a group of rare tumors mainly generated from disorder proliferation of the trophoblast cells resulting from pregnancy. Women of childbearing age are at a high risk of GTN. Chemotherapy is the most

effective treatment, but its teratogenic effects and reproductive toxicity are major concerns for oncologists.^[1]

Although a series of observational studies found no significant differences in fetal congenital abnormality rates between GTN patients treated with chemotherapy and the general population, most GTN patients used contraceptives for more than one year after treatment.^[2,3] Methotrexate (MTX), actinomycin-D (Act-D), and 5-fluorouracil (5-Fu) are the most commonly used chemotherapy drugs in GTN,^[4,5] and their teratogenic or genetic toxic mechanisms are not clear.

We presented here a case of a 33-year-old female diagnosed with GTN who received 5-Fu + Act-D chemotherapy, became pregnant the month after the last course of treatment, and delivered a full-term baby without deformities or abnormal growth and development. Informed consent for the release of patient information was obtained for the publication of this case report.

2. Case presentation

The patient was a 33-year-old female who had received suction evacuation of the uterus for an artificial abortion 10 years prior. Unscheduled vaginal bleeding had been ongoing since January 10, 2011, without lower abdominal pain, and the last menstrual period (LMP) was unclear. Ultrasound examination on February 27, 2011, indicated hydatidiform mole, and the blood human chorionic gonadotropin (hCG) level was 924415 mIU/mL.

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Suction evacuation was performed on March 1, 2011, with a pathological diagnosis of partial hydatidiform mole. Because ultrasound indicated residual trophoblastic tissue with blood hCG 14672 mIU/mL, suction evacuation was performed again on March 10, 2011, but no villus tissue was found. After the operation, the minimum blood hCG level was 5869 mIU/mL and it rose again. On April 7, 2011, the blood hCG level was 12285 mIU/mL. Ultrasound showed abnormal echogenicity in uterine intracavitary, and computed tomography (CT) screening indicated multiple lung metastases. Diagnosis therefore favored invasive moles (FIGO Stage III: FIGO Score 5). Considering the high blood hCG level, 2 courses of 5-Fu 26 mg/kg QD and Act-D 6 μ g/kg QD combination chemotherapy were administered for 8 days per treatment course. Because of severe myelosuppression, we reduced the dosage in the following 3 courses, with 6 days per treatment course. The blood hCG level returned to normal with no abnormality on ultrasound or chest CT screening after 3 courses of chemotherapy. The treatment was completed on August 5, 2011.

The patient's LMP was September 13, 2011, and her blood hCG level rose to 63629 mIU/mL on October 13, 2011. Ultrasound examination on November 6, 2011, indicated intrauterine singleton pregnancy of 7⁺ gestational weeks. It was difficult for the patient to get pregnant so she insisted on continuing the pregnancy. Ultrasound on December 15, 2011, indicated 13 weeks of gestation and the fetal nuchal translucency (NT) thickness was 1.53 mm; there were no significant abnormalities on ultrasonographic soft markers. Further fetal abnormal karyotypes in the first trimester of pregnancy showed low risk of trisomy 21, 18, and 13. Prenatal ultrasound screening on February 24, 2012 (23⁺ gestational weeks) indicated 22⁺ weeks of gestation and no significant fetal anomalies. The patient underwent regular obstetrical examinations throughout pregnancy and had a normal full-term delivery. Her male infant showed no deformities or abnormal growth and development after a follow-up of 48 months.

3. Discussion

The fertility of GTN patients is always a major concern for gynecological oncologists, as most patients want children. The use of artificial contraception for at least 1 year is recommended because of the high recurrence rate in the first year after finishing treatment. However, germ cell chromosomal abnormality, which is the short-term effect most likely to occur due to the toxicity of chemotherapy, has not been studied extensively. Two results correlate to germ cell chromosomal abnormality: fetal abnormality and gene mutation-related long-term diseases. Little is known about the former.

In this case, 5-Fu and Act-D were administered. 5-Fu can be synthesized to FdUMP, which principally acts as a thymidylate synthase inhibitor. It causes cells to become dTMP deficient during deoxyribonucleic acid (DNA) replication or incorporates into ribonucleic acid (RNA) during RNA transcription.^[6] Act-D binds to DNA transcription initiation complex, which also inhibits RNA transcription.^[7] Both drugs are able to inhibit protein synthesis, which means that they have little influence on dormant cells such as the primary oocyte. However, when the primary oocyte is recruited 60 to 70 days before forming the secondary follicle, oogenesis and meiosis could be disturbed by 5-Fu or Act-D.

Until recently, research on the reproductive toxicity of chemotherapeutics in GTN treatment was focused on patients'

ovarian function after chemotherapy. Approximately 95% of GTN patients resumed normal menstruation, but menopause occurred earlier than in the general population.^[2] Even multiagent EMA-CO chemotherapy had little effect on menstruation, but it took longer for patients to return to their normal menstrual cycle after multidrug regimens than after a single drug.^[8]

Second, research also focused on the pregnancy outcomes of GTN patients who finished chemotherapy at least 3 months before becoming pregnant. More than 90% of these patients were able to conceive and more than 70% had full-term healthy births, no matter which regimens were chosen. The main complications were second hydatidiform moles and miscarriages, but reports showed no significant differences between GTN patients and the general population.^[2,9,10] Few retrospective studies have reported on fetal malformations resulting from conception after the completion of chemotherapy,^[2,9-11] and the sample sizes were small. Moreover, no data showed the relationship between the duration of artificial contraception and the rate of fetal malformation. As a result, more data are necessary to guide the clinical work.

Further recommendations about the duration of contraception after chemotherapy remain uncertain, which may result in inappropriate induced abortions due to fears of fetal anomaly or genetic abnormality. Based on the follicular development cycle, the effects of the oocytes' exposure to the chemotherapeutic will last at least 3 months. In this case, the patient became pregnant just 1 month after finishing treatment, which indicated that the oocytes had been directly exposed to the chemotherapeutics, with great potential for genetic damage. The patient's pregnancy resulted in a full-term healthy birth, and the baby showed normal development and growth after a follow-up of 48 months. The study of genetic toxicity in humans is difficult due to ethical reasons. According to the results of limited observational studies, fetal anomalies and birth defects after chemotherapy were rare. But the pregnancies mostly occurred more than 3 months after the last course of chemotherapy. This case is the first report on the effects of direct exposure of chemotherapy on genotoxicity, which may provide references for clinical work.

As a result of this case, it is necessary to understand how soon a patient can safely conceive after finishing chemotherapy and the recommendations for prenatal testing.

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