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Case Report / Приказ болесника

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Two cases of uneventful pregnancies following the treatment of choriocarcinoma

Два случаја некомпликоване трудноће након лечења хориокарцинома

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SUMMARY

Introduction Gestational trophoblastic disease represents a distinguished group of disorders that are derived from placental trophoblastic tissue aroused from abnormal fertilization. Choriocarcinoma is a malignant human chorionic gonadotropin-producing epithelial tumor arising from villous trophoblast. The choice of the chemotherapy regime is based on the International Federation of Gynecology and Obstetrics stage and World Health Organisation score of the disease. The aim of this article is to show that successful pregnancy is possible even after treatment of high-risk gestational trophoblastic neoplasia.

Outlines of cases We present two successfully treated patients who achieved pregnancy and delivered healthy babies in term.

Conclusion Gestational trophoblastic neoplasia has become the most curable malignant disease since the introduction of chemotherapy, which is effective and well-tolerated, and allows fertility preservation in high-proportion of women.

Keywords: gestational trophoblastic neoplasia; choriocarcinoma; pregnancy; fertility

САЖЕТАК

Увод Гестацијска трофобластна болест представља групу поремећаја који настају из плацентног трофобластног ткива порекла абнормалне оплодње. Хориокарцином је малигни епителни тумор који производи хумани хориони гонадотропин и настаје из вилозног трофобласта. Избор режима хемиотерапије заснива се на стадијуму Међународне федерације за гинекологију и акушерство и скору болести према Светској Здравственој Организацији. Циљ овог рада је да покаже да је успешна трудноћа могућа и после лечења високо ризичних гестацијских трофобластних неоплазија.

Прикази болесникâ Представљамо две успешно лечене пацијенткиње које су затруднеле и родиле здраве бебе у термину.

Закључак Гестацијска трофобластна неоплазија је постала најизлечивија малигна болест од увођења хемиотерапије, која је ефикасна и добро толерисана и омогућава очување фертилитета код великог броја жена.

Кључне речи: гестациона трофобластна неоплазија; хориокарцином; трудноћа; фертилитет

INTRODUCTION

Gestational trophoblastic disease (GTD) represents a distinguished group of disorders that are derived from placental trophoblastic tissue aroused from abnormal fertilization [1]. The malignant forms of GTD are known as gestational trophoblastic neoplasia (GTN) [2]. Choriocarcinoma is a malignant hCG-producing epithelial tumor arising from villous trophoblast. It is characterized by myometrial invasion, and histologically by specific trophoblastic hyperplasia and anaplasia, absence of formed chorionic villi, and haemorrhage with central necrosis [1]. Human chorionic gonadotropin (hCG), a glycoprotein hormone is an excellent biomarker of disease progression, response to therapy, and post-treatment follow-up instrument [3].

Before the era of chemotherapy these tumors were highly lethal, usually due to the inability to control haemorrhage within the tumor or metastatic site. Indeed, choriocarcinoma is considered one of the most chemosensitive solid tumors, with the cure rates reaching 95% .

The choice of the chemotherapy regime is based on the International Federation of Gynecology and Obstetrics (FIGO) stage (Table 1) and World Health Organization score of the disease [4]. The scoring system prognostic factors are patient's age, antecedent pregnancy, hCG levels, tumor mass size, metastases and previously failed chemotherapy [5] (Table 2). Since the majority of patients are reproductive aged woman, fertility preservation and the outcome of future pregnancies represent one of the major post-treatment issues. Clinic for Gynecology and Obstetrics, University Clinical Centar of Serbia represents the national center for the treatment of GTD. This national center is formed in 2015 by the Ministry of health of Republic Serbia and since then 50 patients were treated; eighteen of them had malignant form of diasease of which thirteen were treated with single- and five with multi-agent therapy.

So here we present two patients successfully treated with multi-agent chemotherapy, who subsequently became pregnant and delivered healthy infants.

REPORTS OF CASES

Case 1

A 24-year-old patient was admitted in December 2015, two weeks after the uterine curettage in a regional hospital due to bleeding and beta-hCG > 250 000 IU/L three months after the delivery (emergency Caesarean section in term pregnancy due to fetal asphyxia). The newborn died few hours after the delivery. The expert pathologist confirmed the diagnosis of choriocarcinoma. Beta-hCG value was 362 958 IU/L. Radiological staging (computed tomography- CT and magnetic resonance imaging- MRI) showed heterogenous mass measuring 61x83x77 *mm* in uterus with the full-thickness myometrial invasion; probable parametrial invasion, as well as the vaginal metastatic lesion measuring 15x12x20 *mm*. The GTD clinical board determined FIGO II stage high-risk disease (FIGO score = 7) and patient was scheduled for the EMA-CO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine) chemotherapy. The patient received nine cycles of chemotherapy until the normalization of the beta-hCG values followed by additional two consolidation cycles. During the post chemotherapy surveillance period no increase in beta-hCG values were noticed during three years. Three years after the last chemotherapy cycle the patient spontaneously conceived. The pregnancy course was uneventful. At the 39th gestational

week a scheduled Caesarean section was done, and the patient delivered a healthy male infant weighing 3760 *g*, Apgar score at 5 minutes was 9. The placenta appeared normal on gross morphological examination, and was sent for histopathologic examination which showed no signs of gestational trophoblastic neoplasia. The beta-hCG values were controlled and reported negative six weeks after the delivery.

Case 2

In April 2017 the 31-year-old patient was hospitalized due to prolonged postpartum bleeding, 40 days after an uneventful vaginal term delivery. Uterine curettage was done in regional hospital two weeks prior to admission and pathology indicated choriocarcinoma. The initial beta-hCG values were 276 070 *IU/L*. The expert pathologist confirmed the diagnosis of choriocarcinoma. Thoracal CT showed three metastatic lesions measuring up to 30 mm and several satellite lesions ranging 5 to 10 *mm*. Abdominal and pelvic MR imaging detected only myomas.

The GTD clinical board determined FIGO III stage and high-risk (FIGO score = 9) disease and EMA-CO chemotherapy commenced. Nine therapy cycles (until the normalization of beta-hCG level) and two consolidation cycles were administered. The levels of beta-hCG remained negative for 27 months. In November 2019 patient spontaneously conceived. The pregnancy course was uneventful. Elective Caesarean section was done in the 38th gestational week and patient gave birth to a healthy female infant weighing 3170 *g*, Apgar score at 5 minutes 9. Both the macroscopical and microscopical histological examination of the placenta were normal. Beta-hCG level was negative six weeks after the delivery.

These reports were approved by the institutional ethics committee, and written consent was obtained from the patients for the publication of the reports and any accompanying images.

DISCUSSION

Choriocarcinoma is a pregnancy associated tumor and can arise after any type of pregnancy; about 50% follows molar pregnancy, and the other half occurs with similar frequency after a spontaneous abortion or ectopic pregnancy, or after a term or preterm gestation [1]. The diagnosis of choriocarcinoma and other malignant entities within GTD can be challenging, with abnormal vaginal bleeding and elevated bhCG values being the hallmarks of the clinical presentation. [3]. In the two cases described, choricarcinoma was preceded by term pregnancies. Both patients complained of prolonged postpartal vaginal bleeding, and the diagnosis was confirmed histologically after the uterine curettage.

The advent of chemotherapy has changed the prognosis of GTN dramatically. The therapy is instituted based upon the FIGO risk score, which takes into account the age of the patient, the type of and the time interval from the antecedent pregnancy, value of the pretreatment hCG, number and site of the metastases, the size of the largest tumor mass and the response to the prior chemotherapy, with high-risk patients (FIGO score ≥ 7) being treated with multi-agent protocol. The multi-drug chemotherapy scheme of choice for the treatment of high-risk GTN is a combination of etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (EMA/CO) first introduced in 1979 [6]. Both of our patients were high-risk so they were treated with multi-agent chemotherapy (EMA-CO).

Given the fact that most GTN patients are women of reproductive age, with excellent prognosis and long-term survival rates after the chemotherapy treatment, the attention is directed towards long term effects of chemotherapy on the ovarian function, future fertility, risk of premature menopause and the possible mutagenic and teratogenic effects [7, 5]. Ovarian function may be influenced by the chemotherapeutical agents. It has been shown that the levels of Anti-Mullerian hormone (AMH), the marker of ovarian reserve, are decreased after the administration of etoposide-based chemotherapy for the GTN, in comparison to the patients with hydatifom mole that did not receive chemotherapy [8]. Transient amenorrhoea, another sign of the disturbed ovarian function as a consequence of the chemotherapy, is occasionally seen in patients with GTN [9, 5]. In the majority of women, generally, the normal menstrual cycle is recovered and there is no significant fertility compromise. Our two patients recovered mensturual cycle 30-40 days after the end of treatment. The conception rate in treated patients varies between 69 and 86% and is comparable to the one of general population [7]. Although some studies questioned increased miscarriage rates among patients who previously received

chemotherapy for GTN, it was mainly associated with the conception within the first year after completed treatment [10, 11]. First important aspect is the timing of the pregnancy. Our patients were suggested to use some of contraceptive methods in order to postpone pregnancy at least one year after treatment. As the disease recurrence monitoring is based on the hCG surveilance, an increase of this hormone associated with pregnancy may compromise adequate follow-up. There is a concern of the direct teratogenic effect of the chemotherapeutic agents. Knowing the duration of the oocyte maturation cycle, it may be concluded that the effect of chemotherapy lasts at least three months. Indeed, results of a Japanese study reported an increased risk of abnormal pregnancy outcomes (spontaneous abortion, still birth, repeat mole) in patients who conceived within six months of completing chemotherapy for GTN [12].

Therefore, one year appears to be a reasonable time interval from the treatment completion to the next pregnancy; it allows for the timely detection of the early recurrences and minimizes the teratogenic risk. Both single- and multi-agent chemotherapy can be safely administered to patients with a desire for childbearing [5]. In most studies women who registered live birth were mostly younger age (< 40 age) [11]. Both of our patients were also younger age. Most women with gestational trophoblastic neoplasia are cured, but there is still a small and rare group who is refractory to all standard chemotherapy regimens, and it is called ultra-high risk GTN. For this group of patients, high-dose chemotherapy with peripheral blood stem cell support can be an option but recovery of ovarian function is very rare, and actually there have been no pregnancies described. In group of low-risk GTN pregnancy rate is similar to general population. In our Clinic from 18 GTN patients, 5 of them were resistant to single agent therapy and the others were not, which matches with data that about ¾ patients are actually low-risk [13].

In conclusion, except for the risk of ovarian reserve damage, and, rarely, possible premature ovarian failure, multiagent chemotherapy can be safely administered to the patients with desire of future childbearing. The pregnancy should be deferred for at least one year after the treatment completion. Gestational trophoblastic neoplasia has become the most curable malignant disease since the introduction of chemotherapy, which is effective and well-tolerated, and allows fertility preservation in high-proportion of women as it is shown in our two cases [14, 15].

Conflict of interest: None declared.

REFERENCES

1. Clark JJ, Slater S, Seckl MJ. Treatment of gestational trophoblastic disease in 2020s. Curr Opin Obstet Gynecol. 2021; 33(1):7-12. doi: 10.1097/GCO.0000000000000674, PMID: 33337613.
2. Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan KP et al. Diagnosis and management of gestational trophoblastic disease: 2021 update. Int J Gynecol Obstet. 2021; 155 (Suppl 1): 86-93. doi:10.1002/ijgo.13877, PMID: 34669197.
3. Silva ALMD, Monteiro KDN, Sun SY, Borbely AU. Gestational trophoblastic neoplasia: Novelties and challenges. Placenta. 2021; 116:38-42. doi: 10.1016/j.placenta.2021.02.013, PMID:33685753.
4. Bolze PA, You B, Lotz JP, Massardier J, Gladieff L, Joly F et al. Successful pregnancy in a cancer patient previously cured of a gestational trophoblastic tumor by immunotherapy. Ann Oncol. 2020; 31(6): 823-825. doi:10.1016/j.annonc.2020.02.015, PMID: 32171750.
5. Cioffi R, Bergamini A, Gadducci A, Giorgione V, Petrone M, Rabaiotti E et al. Reproductive Outcomes After Gestational Trophoblastic Neoplasia. A Comparison Between Single-Agent and Multiagent Chemotherapy: Retrospective Analysis From the MITO-9 Group. Int J Gynecol Cancer. 2018;28(2):332-337. doi: 10.1097/IGC.0000000000001175, PMID: 29324534.
6. Balachadran K, Salawu A, Ghorani E, Kaur B, Sebire NJ, Short D et al. When to stop human chorionic gonadotropin (hCG) surveillance after treatment with chemotherapy for gestational trophoblastic neoplasia (GTN): A national analysis on over 4,000 patients. Gynecol Oncol. 2019; 155(1): 8-12. doi: 10.1016/j.ygyno.2019.07.024, PMID: 31375268.
7. Ngu SF, Ngan HYS. Surgery including fertility sparing treatment of GTD. Best Pract Res Clin Obstet Gynaecol. 2021; 74:97-108. doi: 10.1016/j.bpobgyn.2020.10.005. PMID: 33127305.
8. Iwase A, Sugita A, Hirokawa W, Goto M, Yamamoto E, Takikawa S et al. Anti-Müllerian hormone as a marker of ovarian reserve following chemotherapy in patients with gestational trophoblastic neoplasia. Eur J Obstet Gynecol Reprod Biol. 2013;167(2):194-8. doi: 10.1016/j.ejogrb.2012.11.021, PMID: 23274042.
9. Spears N, Lopes F, Stefansdottir A, Rossi V, De Felici M, Anderson RA et al. Ovarian damage from chemotherapy and current approaches to its protection. Hum Reprod Upadate. 2019; 25(6): 673-693. doi: 10.1093/humupd/dmz027, PMID: 31600388.
10. Gerstl B, Sullivan E, Vallejo M, Koch J, Johnson M, Wand H et al. Reproductive outcomes following treatment for a gynecological cancer diagnosis: a systematic review. J Cancer Surviv. 2019; 13(2): 269-281. doi: 10.1007/s11764-019-00749-x, PMID: 30997658.
11. Lok C, van Trommel N, Massuger L, Golfier F, Seckl M; Practical clinical guidelines of the EOTTD for treatment and referral of gestational trophoblastic disease. Eur J Cancer. 2020; 130:228-240. doi: 10.1016/j.ejca.2020.02.011, PMID: 32247260.
12. Matsui H, Iitsuka Y, Suzuka K, Yamazawa K, Tanaka N, Seki K et al. Risk of abnormal pregnancy completing chemotherapy for gestational trophoblastic tumor. Gynecol Oncol 2003;88(2):104-7. doi: 10.1016/s0090-8258(02)00071-9, PMID: 12586587.
13. Joneborg U, Coopmans L, van Trommel N, Seckl M, Lok CAR, Fertility and pregnancy outcome in gestational trophoblastic disease, Int J Gynecol Cancer 2021; 31(3): 399-411. doi: 10.1136/ijgc-2020-001784, PMID: 33649007.
14. Li Y, Kong Y, Wan X, Feng F, Ren T, Zhao J et al. Results with Floxuridine, Actinomycin D, Etoposide, and Vincristine in Gestational Trophoblastic Neoplasias with International Federation of Gynecology and Obstetrics Scores ≥5. Oncologist. 2021; 26(12): e2209-e2216. doi: 10.1002/onco.13943. PMID: 34396643.
15. Hancock BW, Tidy J. Placental site trophoblastic tumour and epithelioid trophoblastic tumour. Best Pract Res Clin Obstet Gynaecol. 2021;74:131-148.doi: 10.1016/j.bpobgyn.2020.10.004, PMID: 33139212.

Table 1. International Federation of Gynecology and Obstetrics stages of the disease

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs with or without known genital tract involvement
Stage IV	All other metastatic sites

GTN – gestational trophoblastic neoplasia

Table 2. The scoring system prognostic factors

Scores	0	1	2	4
Age	< 40	≥ 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval from index pregnancy (months)	< 4	4 – < 7	7 – < 13	≥ 13
Pre-treatment serum hCG (IU/ml)	$< 10^3$	10^3– $< 10^4$	10^4 – $< 10^5$	$\geq 10^5$
Largest tumor size (including uterus)	-	3-<5 cm	≥ 5 cm	
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastases	-	1–4	5–8	> 8
Previous failed chemotherapy	-	-	Single drug	2 or more drugs

hCG – human chorionic gonadotropin

