Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(2) 673–681

DOI: 10.1177/0300060518807600
journals.sagepub.com/home/imr
SAGE

False diagnosis of and needless therapy for presumed gestational trophoblastic disease in women with an unusual site of residual pregnancy

Tong Gao[1,2], Mingming Sun[1,2], Liangqing Yao[1,2] and Wei Jiang[1,2]

Abstract

Objective: This study aimed to determine the diagnostic value of magnetic resonance imaging (MRI), hysteroscopy, and laparoscopy to avoid unnecessary treatment when patients present with clinical manifestations that are close to those of gestational trophoblastic neoplasia (GTN).

Methods: Three patients who were falsely diagnosed with presumed GTN and received needless chemotherapy in our hospital from July 2011 to March 2012 were studied. We also reviewed data of patients with similar clinical features who were diagnosed as having residual pregnancy in recent years. Clinical manifestations were evaluated.

Results: All three patients had persistently high serum β-human chorionic gonadotrophin levels and a mass with abundant blood supply in the uterus after termination of pregnancy. The patients were diagnosed with GTN and underwent chemotherapy. They responded poorly to chemotherapy and underwent surgery. The pathological diagnosis in all patients was residual pregnancy. In recent years, no patients were misdiagnosed because pelvic MRI, hysteroscopy, or laparoscopy was used when residual pregnancy could not be excluded.

Conclusion: Gynecologists should diagnose carefully when patients present with clinical manifestations that are close to those of GTN to avoid unnecessary treatment. MRI, hysteroscopy, and laparoscopy could be important examinations for excluding residual pregnancy.

[1]Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China
[2]Shanghai Key Laboratory of Female Reproductive Endocrine Related Diseases, Shanghai, China

Corresponding author:
Wei Jiang, Department of Gynecology, Obstetrics and Gynecology Hospital, Fudan University, 419 Fangxie Road, Shanghai, 200011, China.
Email: jw52317@126.com

Keywords
Gestational trophoblastic neoplasia, false diagnosis, magnetic resonance imaging (MRI), hysteroscopy, laparoscopy, β-human chorionic gonadotrophin (hCG), residual pregnancy

Date received: 27 June 2018; accepted: 26 September 2018

Introduction

Gestational trophoblastic neoplasia (GTN), known as "God's first cancer and man's first cure", refers to a group of malignant diseases, including invasive moles, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. Chemotherapy is the primary treatment for gestational trophoblastic tumor, and the majority of women with GTN are cured with their initial chemotherapy treatment.[1] Malignant trophoblastic disease is a rare tumor that can be cured, even in the presence of widespread metastasis. GTN is the only solid tumor that does not require pathological diagnosis. Diagnosis of GTN is made according to patients' clinical symptoms, serum β-human chorionic gonadotrophin (hCG) tests, and imaging findings.

Ectopic pregnancies account for 1.5% to 2% of all pregnancies, and approximately 10% of ectopic pregnancies implant in nontubal locations. These nontubal locations include the abdominal cavity, cervix, ovary, interstitial portion of the fallopian tube, broad ligament, the uterine cornua, or within a cesarean section scar. Cornual pregnancy accounts for only 0.27% of all ectopic pregnancies.[2] Therefore, there has been limited experience with management of cornual pregnancies. Retained intrauterine trophoblastic tissue is not uncommon. This can lead to continuous bleeding, infection, and late complications, including intrauterine adhesions and infertility.

Clinically, distinguishing the diagnosis of GTN and an unusual site of residual pregnancy by nonspecific clinical features is difficult. Therefore, we performed a retrospective study of three patients who were falsely diagnosed and had needless chemotherapy in our hospital. We aimed to assess how to avoid false diagnosis of and needless therapy for presumed gestational trophoblastic disease (GTD) in women with an unusual site of residual pregnancy.

Method

In this study, retrospective analysis was used to study three falsely diagnosed patients with presumed GTN who received needless therapy from July 2011 to March 2012 in the Obstetrics and Gynecology Hospital of Fudan University. The Institutional Ethical Board of our hospital approved the use of the patients' medical records (No: 2018-50). The patients provided written informed consent. The patients had persistently high serum β-hCG levels and a mixed echogenic mass in the uterus after termination of pregnancy. We also analyzed the clinical features of patients with the same symptoms who were diagnosed with residual pregnancy in recent years. Clinical manifestations, biochemical analysis, and treatment were evaluated.

Results

After carefully reviewing all of the patients with initially suspected GTN who were finally diagnosed as having residual pregnancy in recent years, we found that none of the patients received unnecessary chemotherapy. All of the patients (n = 221)

underwent pelvic magnetic resonance imaging (MRI), or hysteroscopic or laparoscopic evaluation from 1 January 2013 to 1 January 2018. Summaries of case histories for the three women who were incorrectly diagnosed with GTN are shown in Table 1. The patients had persistently high serum β-hCG levels and mixed echogenic masses in the uterus on pelvic ultrasonography after termination of pregnancy. All of the patients were initially suspected of having GTD, needlessly underwent major chemotherapy, and later were found to have residual pregnancy or placental implantation. Detailed histories for the patients are described below.

Patient 1

A 27-year-old, gravida 3, para 1, abortion 2 woman underwent an artificial abortion at 10 weeks of gestation. A pathological examination showed placental tissue. She had vaginal bleeding after the operation. Pelvic ultrasonography showed a mixed echogenic mass that was 10×8 mm and located within the uterine cavity. The patient received half a pill of mifepristone once a day for 2 weeks. However, this treatment was ineffective, and she subsequently underwent a second dilation and curettage for a presumed residual pregnancy. Her menstruation was absent after the operation. Pelvic ultrasonography showed endometrial cavity fluid and an open vascular plexus of the myometrium. The serum β-hCG level reached 331.51 mIU/mL (Figure 1). Therefore, the patient then underwent mifepristone treatment, with half a pill once a day for 1 month. β-hCG levels were slightly decreased, but a repeat ultrasonography showed a mixed echogenic mass of $42 \times 35 \times 35$ mm that was located within the right horn of the uterus with an

Table 1. Summary of case histories.

Patient	1	2	3
Age (years)	27	36	42
Number of pregnancies	4	3	3
Parity	1	2	1
Pattern of terminating previous pregnancy	Artificial abortion	Artificial abortion	Artificial abortion
Weeks of termination of previous gestation	10	6	6
Residual site	Right uterine horn	Left uterine horn	Uterine myometrium
Mass size in ultrasonography	$36 \times 34 \times 31$ mm	$49 \times 46 \times 45$ mm	$49 \times 49 \times 37$ mm
Suspicious lesions outside of the uterus	Multiple pulmonary nodules in computed tomography	None	None
FIGO staging and scoring	III:4	I:8	I:4
Chemotherapy	Four courses of KSM	Six courses of EMA-Co	Two courses of MTX
Surgical treatment	Laparoscopic cornual resection	Abdominal excision of uterine focus	Curettage guided by B ultrasound
Pathological diagnosis	Cornual pregnancy residue	Placental implantation	Cornual pregnancy residue

The mass size in ultrasonography indicates the mass size before chemotherapy. FIGO, International Federation of Gynecology and Obstetrics; KSM, Kengshengmycin; EMA-Co, etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine/oncovine; MTX, methotrexate.

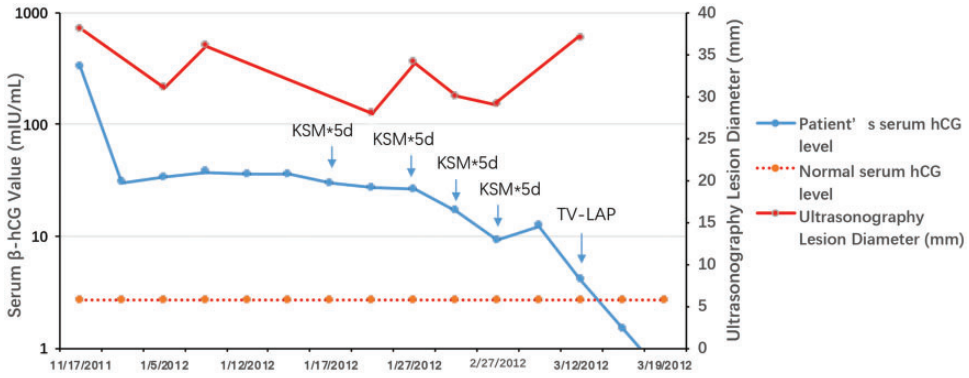

Figure 1. Human chorionic gonadotrophin levels, lesion diameter by ultrasonography, and intervention in Patient 1.

abundant blood supply. β-hCG levels plateaued at 30 to 40 mIU/mL. A chest radiograph and computed tomography showed multiple pulmonary nodules that had clear boundaries and uniform density. Lung metastasis of the tumor could not be excluded. MRI showed an intramural mass on the right cornua with mixed signals on T1-weighted imaging (T1-WI) and T2-weighted imaging (T2-WI). GTD was considered first. According to International Federation of Gynecology and Obstetrics (FIGO) 2000,[3] she was diagnosed with GTN (III:4) and underwent four courses of Kengshengmycin (500 μg/d intravenous drip for 5 days) for 2 weeks. β-hCG levels initially decreased, but then plateaued at 9.12 to 12.38 mIU/mL. The mass size on ultrasound remained at $29 \times 28 \times 27$ mm after Kengshengmycin treatment. The pulmonary nodules also showed no evident change. Because of a minimal reduction in mass size, the decision was made to perform laparoscopic cornual resection. A pathological examination showed broken fibers of smooth muscle tissue, and a small number of trophoblast cells were observed in some highly degenerative tissue. Immunohistochemistry showed AE1/AE3(+++), HCG(+), human placental lactogen(+++), inhibin-a(+), p53(−), and ki-67(−). Pathological reports showed that the tissue was residual pregnancy. A follow-up 1 week after discharge showed that the patient's β-hCG level had returned to normal (<2.67 mIU/mL) and the pulmonary nodules had no significant change on our follow-up visit.

Patient 2

A 36-year-old, gravida 3, para 2, abortion 1 woman underwent an artificial abortion because of increased vaginal bleeding. A pathological examination showed decidual tissue. Two weeks after the operation, the serum β-hCG level was > 10,000 mIU/mL (Figure 2). Pelvic ultrasonography showed a mixed echogenic mass of $50 \times 47 \times 45$ mm that was located within the uterine cavity close to the left uterine horn with an abundant blood supply. Chest radiography was negative for pulmonary metastasis. According to FIGO 2000, she was diagnosed with GTN (I:8) and underwent six courses of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine/oncovine chemotherapy for 1 week. The β-hCG level initially decreased to 1.58 mIU/mL, but the mass size in ultrasonography remained at

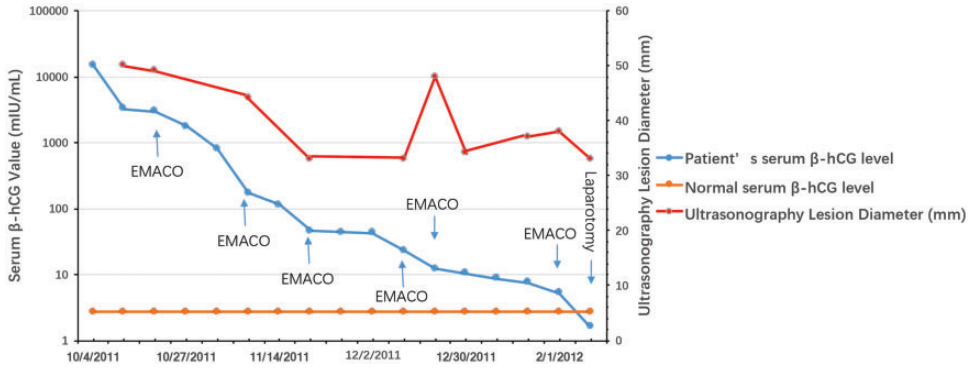

Figure 2. Human chorionic gonadotrophin levels, lesion diameter by ultrasonography, and intervention in Patient 2.

$33 \times 32 \times 31$ mm after this treatment. Because of a minimal reduction in mass size and the evident side effects of chemotherapy, including severe bone marrow suppression, the decision was made to perform an exploratory laparotomy. The lesion tissue was sectioned and sent for pathological examination. A pathological examination showed placental implantation.

Patient 3

A 42-year-old, gravida 3, para 2, abortion 1 woman underwent an artificial abortion at 6 weeks of pregnancy. A pathological examination showed villus tissue. She had irregular vaginal bleeding after the operation, and pelvic ultrasonography showed a mixed echogenic mass of $49 \times 49 \times 37$ mm that was located within the uterine cavity with an abundant blood supply. The β-hCG level was 439 mIU/mL (Figure 2). According to FIGO 2000, she was diagnosed with GTN (I:4) and underwent two courses of methotrexate (20 mg/d intramuscularly for 5 days) chemotherapy for 2 weeks.

The β-hCG level was decreased to 15.61 mIU/mL after chemotherapy, but the mass size on ultrasonography showed no evident change. Therefore, the patient underwent curettage guided by B ultrasound for presumed ectopic residual pregnancy. A pathological examination showed highly degenerated villi. The patient's β-hCG level was 1.60 mIU/mL on the day after the operation.

Discussion

GTN is the only solid tumor that does not require pathological diagnosis. The cure rate of GTN is almost 100%, and preservation of fertility is usually possible with individualized management based on careful scoring and multidisciplinary team planning. Therefore, early diagnosis of GTD is important for successful treatment. The clinical presentation of GTN is variable and nonspecific.[4] Most patients with GTN present with an enlarged uterus, vaginal bleeding, and persistence of theca lutein cysts in the ovaries. GTN metastases occur hematogenously and by spreading to the lungs (80%), vagina (30%), brain (10%), and liver (10%).[5–8] Most of these patients do not obtain a pathological and histological diagnosis. The recent diagnosis of GTD mainly refers to continuously increasing or slowly decreasing hCG levels after pregnancy with a mass with abundant blood supply on ultrasonography.

Serum β-hCG levels provide an important basis for diagnosis. Current FIGO criteria for diagnosis of postmolar GTN are shown in Table 2. As shown in Figures 1, 2, and 3, all three patients had persistently high serum β-hCG levels for several weeks after termination of pregnancy.

Ultrasound is an important aid for diagnosing GTD. Ultrasound images show a myometrial mass that may be uniformly echogenic or hypoechoic, or complex and multicystic.[9,10] Anechoic spaces within the mass may be due to hemorrhagic or necrotic tissue, cysts, or vascular spaces. On color Doppler ultrasound, the lesions usually demonstrate chaotic vascularity with color aliasing and loss of vessel discreteness.[11–13] However, these Doppler features are not specific to GTD. The three patients in our study all received ultrasonic examinations. We observed space-occupying lesions with an abundant blood supply that shared some characteristics of GTD and contributed to our false diagnosis.

In addition to serum HCG levels and ultrasound, MRI plays an important role in diagnosing gestation-associated disease, including an unusual site of pregnancy, residual pregnancy, and GTD. MRI provides correct discrimination of the soft

Table 2. Current International Federation of Gynecology and Obstetrics criteria for diagnosis of gestational trophoblastic neoplasia.

	hCG	Histological diagnosis
1	The plateau of hCG lasts for four measurements over a period of 3 weeks or longer	–
2	Rise in hCG levels of three weekly consecutive measurements or longer, over at least a period of 2 weeks or longer	–
3	Levels of hCG remain elevated for 6 months or longer	–
4	–	There is a histological diagnosis of choriocarcinoma

hCG, human chorionic gonadotrophin.

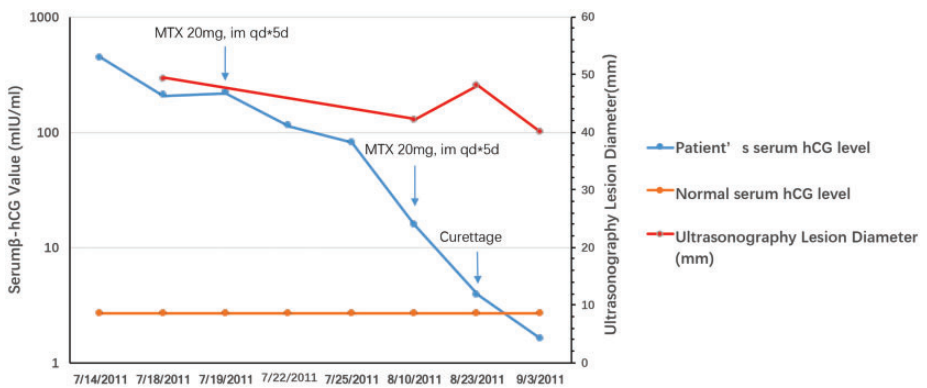

Figure 3. Human chorionic gonadotrophin levels, lesion diameter by ultrasonography, and intervention in Patient 3.

tissue.[14] Srisajjakul[15] et al reported MRI images of cornual pregnancy. They showed that the gestational sac is eccentrically located and is surrounded by a rim of myometrium that is located more than 1 cm from the lateral wall of the endometrial cavity. Fang et al and other authors[16,17] reported that ectopic pregnancy usually has clear boundaries. In these studies, MRI-enhanced scanning showed that the lesion had a clear limit from the surrounding myometrial tissue, but GTD could not be separated from the surrounding tissue. MRI features of GTD of the pelvis always show the following. (1) There is an enlarged uterus and a mass in the uterus or myometrium of the uterus without a clear capsule. (2) MRI shows a heterogeneous mass with a slightly longer T1 and long T2 signal, and the inside or intensive border of the mass has patchy short T1 and short T2 hemorrhagic tissue. (3) There is a discontinuous signal of the endometrium and no clear border between the endometrium and myometrium; the myometrium is always invaded by the mass. (4) Persistent enhancement is found by an enhanced scan and separation, and mass-like enhancement can be detected. (5) There are many thick and round blood vessels in the mass or uterus. (6) Pelvic implantation and ovarian metastasis can be found in GTD, but inguinal and pelvic lymph node metastases are rare. On the basis of the findings of our cases, we believe that MRI has limited effects for detecting GTD. Patient 1 underwent pelvic MRI, which showed an intramural mass on the right cornua with mixed signals on T1-WI and T2-WI. The first impression of the radiologist was that GTD should be considered first. Therefore, the accuracy of MRI in diagnosing GTD may vary according to the experience of the radiologist.

Hysteroscopic management of ectopic pregnancies and residual trophoblastic tissue is safe and efficient.[18–20] Early in 1984, Suzuki et al.[21] reported that hysteroscopy appeared to be a useful aid in confirming complete evacuation of hydatidiform mole. Feng et al.[22] reported that hysteroscopy and laparoscopy were effective alternatives for differentiation of GTN from non-GTN and could also offer therapeutic treatment. Some gynecological oncology doctors are concerned that hysteroscopy may help promote cancer cell metastasis. Li et al.[23] believed that when infusion pressure was lower than 100 mmHg and the operation time was shorter, expansion of uterine fluid into the abdominal cavity and malignant tumor cell growth could probably be reduced. There was no evidence that hysteroscopy caused implantation and metastasis of GTN. Xiang et al.[24] believed that patients who are treated by hysteroscopy should have a frozen section examination to avoid possible GTN metastasis. None of our three patients underwent hysteroscopy during treatment.

The possible causes of misdiagnosis of our patients could be as follows. Residual pregnancy has similar signs and symptoms as GTD, including abnormal vaginal bleeding, an enlarged uterus, previous dilatation and curettage, persistent positive β-hCG levels, and ultrasonography showing space-occupying lesions in the uterus without gestational sacs. Repeated curettage cannot remove residual pregnancy in atypical sites such as cornual pregnancies. One patient even had suspected pulmonary metastasis with nodules in her lungs.

After carefully reviewing all of the patients with initially suspected GTN who were finally diagnosed as having residual pregnancy in recent years, we found that none of the patients received unnecessary chemotherapy. All of the patients underwent pelvic MRI, or hysteroscopic or laparoscopic evaluation. We believe that MRI, hysteroscopy, and laparoscopy could be important examinations for GTN when an ultrasound examination is inconclusive.

In conclusion, our study shows that distinguishing an unusual site of residual pregnancy from GTN is difficult. Hopefully our experience can provide some suggestions for similar cases. When patients show a history, symptoms, and signs that resemble those of GTN, MRI, hysteroscopy, and laparoscopy could be important auxiliary examinations to exclude residual pregnancy.

Acknowledgments

We thank Dr. Xin Lu for her kind help during writing the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research was supported by grants from the Development Fund for Shanghai Talents (2016–2018), the Development Fund for Shanghai Talents, and the Shanghai Funding Program for the Training of Outstanding Young Medical Talents (2016–2018) to Wei Jiang.

References

1. Stevens FT, Katzorke N, Tempfer C, et al. Gestational trophoblastic disorders: an update in 2015. *Geburtshilfe Frauenheilkd* 2015; 75: 1043–1050.
2. Dolinko AV, Vrees RA and Frishman GN. Nontubal ectopic pregnancies: overview and treatment via local injection. *J Minim Invasive Gynecol* 2018; 25: 287–296.
3. FIGO Committee on Gynecologic Oncology. Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. *Int J Gynecol Obstet* 2009; 105: 3–4.
4. Berkowitz RS and Goldstein DP. Current management of gestational trophoblastic diseases. *Gynecol Oncol* 2009; 112: 654–662.
5. Biscaro A, Braga A and Berkowitz RS. Diagnosis, classification and treatment of gestational trophoblastic neoplasia. *Rev Bras Ginecol Obstet* 2015; 37: 42–51.
6. Lurain JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *Am J Obstet Gynecol* 2010; 203: 531–539.
7. Goldstein DP and Berkowitz RS. Current management of gestational trophoblastic neoplasia. *Hematol Oncol Clin North Am* 2012; 26: 111–131.
8. Khoo SK, Sidhu M, Baartz D, et al. Persistence and malignant sequelae of gestational trophoblastic disease: clinical presentation, diagnosis, treatment and outcome. *Aust N Z J Obstet Gynaecol* 2010; 50: 81–86.
9. Allen SD, Lim AK, Seckl MJ, et al. Radiology of gestational trophoblastic neoplasia. *Clin Radiol* 2006; 61: 301–313.
10. Wang CM, Dixon PH, Decordova S, et al. Identification of 13 novel NLRP7 mutations in 20 families with recurrent hydatidiform mole: Missense mutations cluster in the leucine-rich region. *J Med Genet* 2009; 46: 569–575.
11. Kani KK, Lee JH, Dighe M, et al. Gestatational trophoblastic disease: multimodality imaging assessment with special emphasis on spectrum of abnormalities and value of imaging in staging and management of disease. *Curr Probl Diagn Radiol* 2012; 41: 1–10.
12. Taylor KJ, Schwartz PE and Kohorn EI. Gestational trophoblastic neoplasia: diagnosis with doppler US. *Radiology* 1987; 165: 445–448.
13. Desai RK and Desberg AL. Diagnosis of gestational trophoblastic disease: Value of endovaginal color flow Doppler sonography. *AJR Am J Roentgenol* 1991; 157: 787–788.
14. Lin EP, Bhatt S and Dogra VS. Diagnostic clues to ectopic pregnancy. *Radiographics* 2008; 28: 1661–1671.
15. Srisajjakul S, Prapaisilp P and Bangchokdee S. Magnetic resonance imaging in tubal and non-tubal ectopic pregnancy *Eur J Radiol* 2017; 93: 76–89.
16. Fang BD, Chen MK, Yao QD, et al. [Diagnostic value of magnetic resonance imaging in special-site ectopic pregnancy]. *Zhonghua Yi Xue Za Zhi* 2013; 93: 2315–2317.

17. Dai M, Fang BD and Yan ZH. Clinical value of magnetic resonance imaging in gestational trophoblastic tumor. *Journal of Practical Obstetrics and Gynecology* 2011; 27: 814–815.
18. Faivre E, Deffieux X, Mrazguia C, et al. Hysteroscopic management of residual trophoblastic tissue and reproductive outcome: a pilot study. *J Minim Invasive Gynecol* 2009; 16: 487–490.
19. Pan Y and Liu M. The value of hysteroscopic management of cesarean scar pregnancy: a report of 44 cases. *Taiwan J Obstet Gynecol* 2017; 56: 139–142.
20. Bettocchi S, Nappi L, Ceci O, et al. What does 'diagnostic hysteroscopy' mean today? The role of the new techniques. *Curr Opin Obstet Gynecol* 2003; 15: 303–308.
21. Suzuki A, Kawaguchi K, Konishi I, et al. [Role of hysteroscopy in diagnosis and management of trophoblastic disease]. *Nihon Sanka Fujinka Gakkai Zasshi* 1984; 36: 255–260 [in Japanese, English Abstract].
22. Feng FZ, Xiang Y, He HJ, et al. [Value of hysteroscopy and laparoscopy in differential diagnosis of gestational trophoblastic neoplasia]. *Zhonghua Fu Chan Ke Za Zhi* 2007; 42: 464–467 [in Chinese, English Abstract].
23. Li F, Jie D, Hai-tao Z, et al. Value of hysteroscopy in differential diagnosis of suspected gestational trophoblastic neoplasia. *Chinese Journal of Obstetrics & Gynecology and Pediatrics (Electronic version)* 2009; 4: 370–372.
24. Xiang Y. On guard against the diagnosis trap of gestational trophoblastic tumor: The 11th national academic conference of Gynecological Oncology Committee of the Chinese Cancer Society, Wuhan, Hubei, 2011[C].