A case of metastasizing invasive hydatidiform mole. Is less - less good? Review of the literature with regard to adequate treatment

A. Honig[1], L. Rieger[1], P. Kristen[1], M. Eck[2], T. Frambach[1], A. Tschammler[3], H. Caffier[1], J. Dietl[1]

[1]Department of Obstetrics and Gynecology, Department of Pathology[2], Department of Radiology[3], University of Wuerzburg (Germany)

Summary

Background: Patients with invasive hydatidiform moles (IHM) have a good prognosis. Even if disease has spread, monocytostatic treatment might be sufficient if the diagnosis has been histologically confirmed. Established classifications divide gestational trophoblastic disease (GTD) including choriocarcinoma into cases with "high" and "low" risk. Without respect to histology "high-risk" cases are recommended to obtain polychemotherapy.

Case: A 40-year-old nullipara underwent hysterectomy for persistent vaginal bleeding after she had already been treated with curettage for hydatidiform mole. An IHM was pathohistologically confirmed. There were no signs of pulmonary spread or other metastases at the time of surgery. Postsurgically persistent ß-hCG levels lead to thorough staging, which revealed multiple pulmonary metastases and a vaginal metastasis. Despite metastasizing GTD with poor prognosis criteria she was treated with single agent therapy. Eight cycles of two weekly methotrexate (MTX) were administered. All sites of metastases responded and our patient is still fine after one year of follow-up.

Conclusion: With respect to this and other reports monochemotherapy can be a reasonable primary treatment for metastatic IHM.

Key words: Gestational trophoblastic disease; Invasive hydatidiform mole; Chemotherapy; Review; Case report.

Introduction

The different forms of gestational trophoblastic disease (GTD) can be defined and related to discrete pathologic aberrations occurring at different stages of trophoblastic differentiation. Some of these lesions are true neoplasms, whereas others represent abnormally transformed placentas with a predisposition for neoplastic transformation of the trophoblast. Invasive hydatidiform moles (IHM) are relatively rare; 10-15% of all hydatidiform moles (HM) become invasive. IHM is characterized by the persistence of villous structures and the potential for invasion and metastasis [1, 2]. Histologically, an invasive mole is characterized by hydropic villi and proliferating trophoblastic epithelium invading the uterine muscle and blood vessels, with associated hemorrhage and tissue necrosis. The neoplasm can penetrate the full thickness of the uterine wall and rupture into the broad ligament or pelvic cavity. This form of GTD has all the features of a malignant tumor, with the exception that its duration of viability is sometimes self-limited. IHM is seldom diagnosed without excising the uterus.

The epidemiology of molar pregnancy varies substantially due to different modes of evaluation in the literature [3-5]. The reported incidence of HM by country varies between 1:85 (Indonesia) to 1:700 (USA) pregnancies [3]. In general the incidence in Asian women seems to be higher and the racial implications of the data were as follows in the study by Matsuura *et al.* - rates per 1,000 pregnancies in Hawaii were eight for Caucasian, 17.5 for Filipinos, 16.5 for Japanese and 7.7 for Hawaiian women [6].

Incidence and risk of malignancy for this entity increases with maternal age. Women less than 20 and especially over 40 years have a greater risk for HM. The second best established risk factor is previous HM. The risk of repetition seems to be 0.5%-2.6% and 33% after two previous moles [7]. The prospects of a live birth after three molar pregnancies are nil and the risk of molar pregnancy increases with the number of previous spontaneous abortions [8, 9]. The parental blood group can be a risk factor. Women with group A or AB blood seem to have a higher risk of HM compared with women with group B or 0 blood [9].

The disease has sometimes a surprising course and there have been reports in which an invasive mole has occurred after menopause [10] and metastases in rather uncommon locations are possible, e.g. the spinal cord [11]. Invasive moles account for 5-15% of molar pregnancies [12]. In contrast to this entity, choriocarcinoma consists of widely invasive proliferating cytotrophoblasts and syncytiotrophoblasts without detectable chorionic villi.

Other forms of GTD according to the modified WHO-classification include complete and partial hydatidiform mole, placental site trophoblastic tumor, epitheloid trophoblastic tumor, exaggerated placental site nodule and placental site nodule, as well as choriocarcinoma, whereby 50% of the last-mentioned develop from hydatidiform moles [13].

Revised manuscript accepted for publication October 3, 2004

Case history

A 40-year-old Caucasian female, 0 gravida, was referred to our hospital with a 3-week history of vaginal bleeding and lower abdominal pain. The patient had no significant past medical history.

On admission her ß-hCG level was increased (800,000 mIU/ml). Gynecological examination revealed an enlarged uterus corresponding to the 14th week of gestation. No other abnormalities were detected. Vaginal ultrasound on admission showed a uterine size of 12 cm x 7 cm x 7 cm with an intrauterine mass of 8 cm x 6 cm x 5 cm without fetal structures. Blood works revealed a hemoglobin of 12.2 g/dl. For vaginal bleeding suction evacuation and curettage were performed.

The curettage specimen demonstrated hydropic swelling and circumferential trophoblastic hyperplasia of chorionic villi, representing a complete hydatidiform mole. One day after curettage her ß-hCG had decreased to 320,000 mIU/ml.

We offered and strongly recommended close ß-hCG-follow-up to her in our outpatient clinic. She refused and was seen on a non-regular basis by a local practioner. In the course of the next four weeks ß-hCG rose from from 300,000 to 753,000 mIU/ml. A diagnosis of gestational trophoblastic neoplasia versus retained molar tissue was considered on readmission. The metastatic workup was negative, vaginal ultrasound revealed an inhomogeneous myometrium and the endometrium presented transparent as if full of holes.

Our patient did not desire to bear children and underwent total abdominal hysterectomy. Preoperative X-rays of the lung and vaginal examination did not reveal any pathological findings. At surgery a ragged irregular partly hemorrhagic mass, infiltrating into the myometrium was found in the cavum uteri. Histopathologically, partly hydropic chorionic villi with marked trophoblastic proliferation deeply invaded the outer part of the myometrium. Many chorionic villi were found within the vascular spaces of the myometrium (Figure 3), therefore choriocarcinoma could be excluded. Histology revealed the typical picture of an invasive mole.

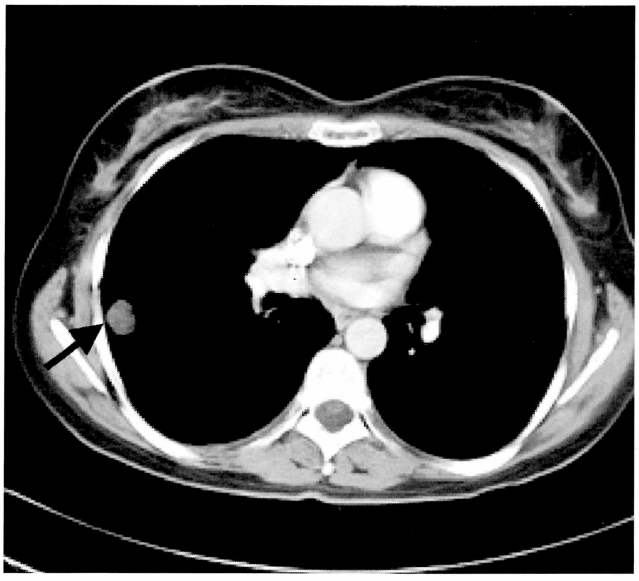
Due to findings of Yang et al. who described a possible significance of p53 and c-erbB2 we also analyzed these markers [14]. The immunohistochemically investigated surgical specimen showed low p53 (focally up to 5% of the trophoblast) and no c-erbB2 expression.

Immediately after surgery ß-hCG showed the expected decline from over 700,000 to below 10,000. Further postoperative ß-hCG follow-up was done by a local gynecologist. Two and a half months later she was referred to our hospital since ß-hCG levels did not fall below 8,000 mIU/ml after hysterectomy.

Workup for GTD and treatment

Staging, consisting of a CT-scan of the head, thorax and abdomen, as well as bone scan, was performed. The CT-scan of the thorax revealed multiple lung metastases on both sides with the biggest shown in Figure 1. Vaginal examination revealed a lesion highly suspicious for a metastasis. The lesion was 2 cm in diameter, of dark blue color, felt hard on palpation and was localized 2 cm under the urethral orifice. All other examinations did not reveal pathological findings.

Methotrexate (MTX) was administered intravenously with 0.5 mg per kg of body weight for five days every two weeks for eight cycles. The ß-hCG levels dropped from 6,000 mIU/ml to 685 mIU/ml two weeks after her first course of chemotherapy. We repeatedly determined ß-hCG levels and the metastasis of the vagina throughout the time the patient was treated in our institution as markers of response to treatment. A marked decrease in size of the vaginal metastasis was already evaluable after the first cycle of MTX chemotherapy. At the time of the fourth chemotherapy cycle vaginal metastasis was no longer palpable. MTX was basically well tolerated, but our patient suffered from mild mucositis. Neither antiemetic nor cortisone supportive therapy was necessary. Before the third cycle of chemotherapy ß-hCG had dropped to 131 mIU/ml and the hormone was no longer detectable after the fifth cycle had been completed. An additional three cycles were administered after the ß-hCG was no longer detectable.



g. 1

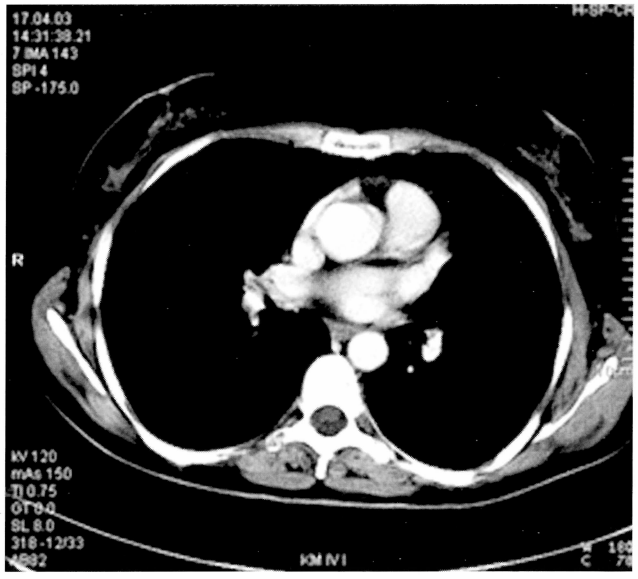


Fig. 2

Figure 1. — Pulmonary metastasis can clearly be seen in the lateral periphery of the lungs on the right side (arrow). CT scan of the thorax before systemic treatment (contrast medium enhanced).
Figure 2. — Same level of thorax CT scan as in Figure 1 after completion of systemic treatment. CT scan of the thorax (contrast medium enhanced).

Restaging after the completion of systemic treatment with a CT-scan of the abdomen and thorax showed that the metastatic lesions had vanished. Only remnants of the lesions in the lung which most probably consisted of fibrotic tissue without the presence of any viable trophoblastic or molar villi cells were still detectable.

The biggest lesion measured 3.5 cm in diameter before the administration of chemotherapy and was undetectable at the end of chemotherapy (Figure 2). We stopped the systemic treatment and started monthly ß-hCG-testing as follow-up. Up until now 12 months after the completion of treatment our patient is without evidence of disease.

Discussion and review of the literature

Clinical classification of GTD

There are numerous classification systems for trophoblastic disease. A comparison of these classification systems revealed that the WHO classification offers the greatest precision in identifying which patients will fail the therapy [15]. We considered both the National Institute of Health (NIH) (Table 1) clinical classification and the WHO prognostic scoring system (Table 2) [16].

Table 1. — *Criteria for poor-prognosis (high risk) metastatic gestational trophoblastic disease.*

NIH criteria:
Urinary hCG excretion > 100,000 IU/24 hours
Duration of disease longer than 4 months (interval since antecedent pregnancy)
Brain or liver metastasis (regardless of disease duration or level of ß-hCG)
Additional poor-prognosis features
Following term pregnancy
Serum ß-hCG > 40,000 mIU/ml
Failed prior chemotherapy
WHO score ≥ 8

Table 2. — *WHO scoring system based on prognostic factors (WHO, 1983).*

Prognostic factor	Prognostic Score*			
	0	1	2	3
Age (years)	< 39	> 39		
Antecedent pregnancy	mole	abortion	term	
Interval between end of antecedent pregnancy and start of chemotherapy (months)	< 4	4-6	7-12	> 12
ß-hCG (mIU/ml)	< 10^3	10^3-10^4	10^4-10^5	> 105
AB = blood groups (female x male)		0 x A A x 0	B AB	
Largest tumor, including uterine (size)		3-5	> 5	
Site of metastases	Lung, vagina, pelvis	Spleen, kidney	Gastrointestinal tract, liver	brain
Number of metastases identified		1-4	4-8	> 8
Prior chemotherapy			Single drug	Two or more drugs

*The total score for a patient is obtained by adding the individual scores for each prognostic factor. Total score less than or equal to 4 = low risk; 5-7 = middle risk; greater than or equal 8 = high risk.

Table 3. — *FIGO staging for GTD.*

Stage
I Disease confined to the uterus
II Beyond uterus but limited to genital structures
III To lungs with or without known genital tract involvement
IV Other metastatic sites - brain, liver etc.

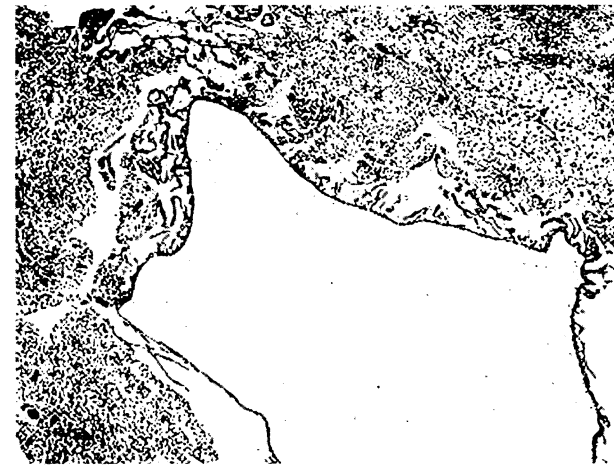


Figure 3. — Invasive hydatidiform mole invading local myometrium (hematoxylin and eosin stained section, 250 x).

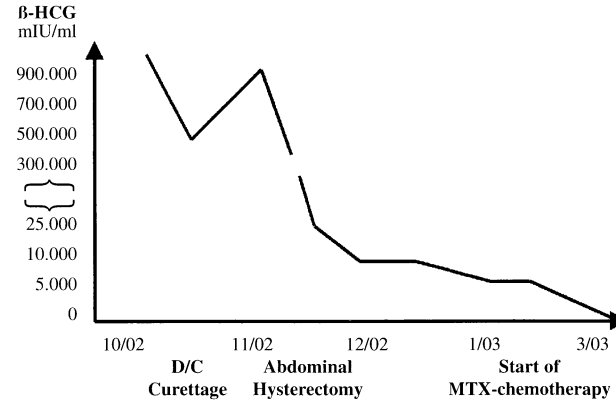


Figure 4. — ß-hCG-levels in the course of surgical and systemic treatment.

Applying the WHO classification systems (Table 2) our patient qualified as a high-risk patient with her individual score adding up to 8 based on age (> 40), ß-hCG (10^3-10^4 mIU/ml), blood group (AB), tumor size (> 5 cm), and number of metastases [1-4] if WHO-criteria were applied [17-19]. Treatment decisions should be based on "high" and "low" risk GTD, but if clear histopathological diagnosis describes invasive mole the chemotherapy might be less aggressive [20].

In retrospect, the immediate administration of chemotherapy for persistent GTD at the time of the patient's hysterectomy may have prevented her pulmonary and vulovaginal recurrence. Being 40 years of age she did not desire to retain reproductive function. In case patients desire future fertility the vast majority of patients with postevacuation persistent GTD will be

cured with a relatively nontoxic single-agent regimen and only 10% will require a hysterectomy [16].

Our case illustrates that workup for metastases is important when treating patients with IHM. Patients frequently do not present with symptoms that lead to the necessary diagnostic tests. Vaginal metastasis is seen in only 4.1% of invasive moles whereas it is twice as common in choriocarcinoma. Instead of significant metastases to the lungs and the genitourinary tract as well as delayed onset of treatment a complete remission was achieved in our patient.

ß-hCG

Even after hysterectomy is performed and IHM is histologically proven adequate follow-up is mandatory to ensure early detection of GTD, which might require local or systemic treatment. In our case follow-up was inadequate. Abnormal bleeding after any gestation should be evaluated promptly with measuring ß-hCG and endometrial sampling. GTD may develop after any gestation including term, ectopic pregnancy or spontaneous abortion. Nevertheless the majority develops after molar pregnancy. A plateau, rise or inadequate decline in ß-hCG levels is an indication for immediate workup for GTD, which also led to the right diagnosis in our patient. The serum ß-hCG is a well-known and excellent indicator for following the process of the disease, checking the effectiveness of treatment, recognizing relapse, progression and adjusting the amount of chemotherapy. A ß-hCG drop as response to the first cycle of chemotherapy of 5- to 10- fold or greater is a good omen, while a decrease of less than 50% is suspicious. The slope of the regression curve of ß-hCG becomes flatter if ß-hCG values reach more normal levels [34].

Immediate ß-hCG follow-up after molar pregnancy should be performed on a twice-weekly basis. If the serum levels once become undetectable recurrences are extremely rare [21]. Pregnancy within one year after GTD is associated with a higher risk of recurrence [22]. Contraception should be ensured for one year to prevent a rise in ß-hCG, whereby data on oral contraceptives with regard to the risk of recurrence is still contradictive [9].

Methotrexate as drug of choice for uncomplicated GTD

Regardless of the histopathology, treatment of metastatic GTD is cytotoxic chemotherapy [20, 23]. Options for monochemotherapy are MTX and dactinomycin [24-26]. Up to 20-30% of tumors are not sensitive to MTX, in which cases polychemotherapy should be offered. Dactinomycin is also used as a compound of polychemotherapy regimens. Etoposide is another possible compound but concern is that it might lead to an increased rate of secondary tumors [27, 28]. A frequently used multi-drug regimen for GTD is EMA/CO with etoposide, methotrexate, adriamycin, cyclophosphamide, and vincristine [29]. Another option that was recommended by Bagshawe for patients with a WHO score of 5, 6, 7 is to apply combination chemotherapy with MTX and dactinomycin with or without cyclophosphamid [30]. Ishizuka and Tomoda applied this dual drug regimen in good prognosis cases at a dose and schedule of MTX 0.4 mg/kg/day IM and dactinomycin 0.01 mg/kg/day IV for five days every three weeks [31].

We and others [20] think that in a case of metastatic invasive mole, a condition that may even regress spontaneously [2], with a generally good prognosis chemotherapy might be less aggressive and not necessarily has to consist of polychemotherapy [9, 32]. Other investigators state that the occurrence of vaginal metastasis qualifies patients as high-risk patients that should subsequently be treated with multiple agent chemotherapy [33]. If a histological diagnosis reveals merely an IHM even high-risk metastatic disease can successfully be treated with single agent regimens such as MTX or dactinomycin as demonstrated in our case. A prerequisite for such an approach is adequate ß-hCG-testing and that metastases can be monitored closely because metastases may represent choriocarcinoma, which follows HM in 3-7% of cases. IHM does not seem to be more complicated by choriocarcinoma than non-invasive mole [34].

MTX is efficacious, has minimal severe toxicity, good cure rates and is cost effective [25, 26, 35]. The drug does not appear to affect fertility. Ninety percent of women trying to conceive became pregnant after MTX therapy in the investigation performed by Khan *et al.* in 2003 [35]. Women who receive polychemotherapy are less likely to have a successful pregnancy [36].

According to Berkowitz *et al.* 40% of patients with metastatic GTD and low-risk disease need alternative therapy to achieve remission after single-agent therapy [37]. In patients with low-risk gestational trophoblastic disease Khan *et al.* documented a complete cure rate without recurrence of 72% and 95% for those who required second-line chemotherapy [35].

Possible complications

Large or multiple vaginal metastases given the fragility and vascularity from invasive mole put a patient at risk for significant hemorrhage and rupture, especially after chemotherapy is given. The most frequent location of such lesions is the anterior wall of the lower part of the vagina [38]. Another risk following abdominal hysterectomy or mole evacuation for an invasive mole is trophoblastic pulmonary embolization. If a patient presents with acute respiratory distress this differential diagnosis should be considered [39].

Pathology

In a recently published report the expression of proteins c-ras, c-erb-B2, nm23 and p53 was correlated with the different entities of hydatidiform moles and gestational trophoblastic disease [14]. The authors were able to show that cases of complete hydatidiform moles that were high in c-erbB-2 and p53 expression and low in nm23 and c-ras expression were most likely to progress to a postmolar tumor. Our results were not consistent with the observation of Yang *et al.* because the molar tissue showed a low expression of p53 but not of the c-erbB-2 gene prod-

ucts and still GTD developed [14]. It suggests that analysis of these gene products might be beneficial but clearly needs further testing.

Survival and prognosis

Since 1975 the overall survival rates based on the data from the New England Trophoblastic Disease Center for Stages I to III are a 100% and approximately 70-73% for Stage IV (Table 3) [40, 41]. Other investigators reported a 100% cure rate in 25 Stage II and 87 Stage III cases compared with a 48% cure rate for 35 Stage IV cases [42]. Our patient qualified for Stage III disease.

References

[1] Danihel L., Zaviacic M., Korbel M., Vojtassak J., Repiska V., Breitenecker G. et al.: "Mole invasia - special form of GTD". *Gen. Physiol. Biophys.,* 1999, *18,* 37.

[2] Tham K.F., Ratnam S.S.: "Current views on the management of tropholastic tumors". *Int. J. Gyn. Obstet.,* 1995, *49,* 77.

[3] Buckley J.D.: "The epidemiology of molar pregnancy and choriocarcinoma". *Clin. Obstet. Gynecol.,* 1984, *27,* 153.

[4] Grimes D.A.: "Epidemiology of gestational trophoblastic disease". *Am. J. Obstet. Gynecol.,* 1984, *150,* 309.

[5] Bracken M.B.: "Incidence and aetiology of hydatidiform mole: an epidemiological review". *Br. J. Obstet. Gynaecol.,* 1987, *94,* 1123.

[6] Matsuura J., Chiu D., Jacobs P.A., Szulman A.E.: "Complete hydatidiform mole in Hawaii: an epidemiological study". *Am. J. Obstet. Gynecol.,* 1982, *89,* 258.

[7] Sand P.K., Lurain J.R., Brewer J.I.: "Repeat gestational trophoblastic disease". *Obstet Gynecol.*, 1984, *63*, 140.

[8] Bagshawe K.D., Dent J., Webb J.: "Hydatidiform mole in England and Wales 1973-83". *Lancet,* 1986, *2*, 673.

[9] Altieri A., Franceschi S., Ferlay J., Smith J., La Vecchia C.: "Epidemiology and aetiology of gestational trophoblastic diseases". *Lancet Oncol.,* 2003, *4,* 670.

[10] Zavadil M., Toman J., Kucera E., Feyereisl J., Safar P., Pan M.: "Proliferating mole in menopause imitating choriocarcinoma recurrence – case report". *Ceska Gynekol.,* 2002, *67,* 278.

[11] Jayaprakash P.G., Ajithkumar T.V., Amma N.S., Nair M.K.: "Metastatic invasive mole causing paraplegia". *Indian J. Cancer,* 1999, *36,* 208.

[12] Palmer J.R.: "Advances in the epidemiology gestational trophoblastic disease". *J. Reprod. Med.*, 1994, *39*, 155.

[13] Shih I.M., Kurman R.J.: "Molecular basis of gestational trophoblastic diseases". *Curr. Mol. Med.,* 2002, *2*, 1.

[14] Yang X., Zhang Z., Jia C., Li J., Yin L., Jiang S.: "The relationship between expression of c-ras, c-erb B-2, nm23 and p53 gene products and development of trophoblastic tumor and their predictive significance for the malignant transformation of complete hydatidiform mole". *Gynecol. Oncol.,* 2002, *85*, 438.

[15] Kohorn E.I.: "The trophoblastic Tower of Babel: classification systems for metastatic gestational trophoblastic neoplasia". *Gynecol. Oncol.*, 1995, *56,* 280.

[16] Lewis J.L. Jr.: "Diagnosis and management of gestational trophoblastic disease". *Cancer,* 1993, *71*, 1639.

[17] Miller D.S., Lurain J.R.: "Classification and staging of gestational trophoblasic tumors". *Obstet. Gynecol. Clin. North. Am.,* 1988, *72,* 413.

[18] Parazzini F., Mangili G., LaVecchia C., Parazzini F., Mangili G., La Vecchia C. *et al.*: "Risk factors for gestational trophoblastic disease: A separate analysis of complete and partial hydatidiform moles". *Obstet. Gynecol.,* 1991, *78*, 1039.

[19] Lurain J.R., Sciarra J.J.: "Study and treatment of gestational trophoblastic diseases at the John I. Brewer Trophoblastic Disease Center, 1962-1990". *Eur. J. Gynaecol. Oncol.*, 1991, *12*, 425.

[20] Van Eijkeren M.A., Sijmons E.A., Witteveen P.O., Verhaar M.J., Sie-Go D.M., Heintz A.P.: "Treatment of metastatic invasive moles in two husband-side sisters-in-law. Case reports and review of literature". *Eur. J. Gynaecol. Oncol.*, 2001, *22,* 406.

[21] Feltmate C.M., Batorfi J., Fulop V., Goldstein D.P., Doszpod J., Berkowitz R.S.: "Human chorionic gonadotropin follow-up in patients with molar pregnancy: a time for reevaluation". *Obstet. Gynecol.,* 2003, *101*, 732.

[22] Zhu L., Song H., Yang X., Xiang Y.: "Pregnancy outcome of patients conceiving within one-year after chemotherapy for gestational trophoblastic tumor: a clinical report of 22 cases". *Chin. Med. J. (Engl.),* 1998, *111,* 1004.

[23] Palmer J.R.: "Advances in the epidemiology gestational trophoblastic disease". *J. Reprod. Med.,* 1994, *39*, 155.

[24] Li M.C., Hertz R., Spencer D.B.: "Successful use of Methotrexate in metastatic gestational trophoblastic disease". *Proc. Soc. Exp. Biol. Med.*, 1956, *93,* 361.

[25] Brewer J.I., Eckman T.R., Dolkart R.E., Torok E.E., Webster A.: "Gestational trophoblastic disease. A comparative study of the results of therapy in patients with invasive mole and with choriocarcinoma". *Am. J. Obstet. Gynecol.,* 1971, *109,* 335.

[26] Hammond C.B., Parker R.T.: "Diagnosis and treatment of trophoblastic disease. A report from the Southeastern Regional Center". *Obstet. Gynecol.,* 1970, *35,* 132.

[27] Jakob A., Kollmannsberger C., Kanz L., Bokemeyer C.: "Late toxicity after chemotherapy of malignant testicular tumors". *Urologe A,* 1998, *37,* 635.

[28] Schorge J.O., Goldstein D.P., Bernstein M.R., Berkowitz R.S.: "Recent advances in gestational trophoblastic disease". *J. Reprod. Med.,* 2000, *45*, 692.

[29] Xiang Y., Yang X., Han S.: "Methotrexate combined chemotherapy for chemorefractory gestational trophoblastic tumour". *Zhonghua Fu Chan K Za Zhi,* 1999, *34,* 97.

[30] Bagshawe K.D.: "Treatment of high risk choriocarcinoma". *J. Reprod. Med.,* 1984, *29,* 813.

[31] Ishizuka N., Tomoda Y.: "Gestational trophoblastic disease: Hydatidiform mole, invasive mole, and choriocarcinoma". Nagoy, Japan, The University of Nagoya Press, 1990.

[32] Khabouze S., Erchidi I.E., Bouchiki C., Chatane A., Kharbach A., Chaoui A.: "Gestational trophoblastic diseases. Apropos of 105 cases". *Gynecol. Obstet. Fertil.,* 2002, *30,* 42.

[33] Goldberg G.L., Yon D.A., Bloch B., Levin W.: "Gestational trophoblastic disease: the significance of vaginal metastases". *Gynecol. Oncol.,* 1986, *24,* 155.

[34] Morrow C.P., Curtin J.P.: Synopsis of Gynecologic Oncology 5th Edition, Churchill Livingstone, 1998, 318.

[35] Khan F., Everard J., Ahmed S., Coleman R.E., Aitken M., Hancock B.W.: "Low-risk persistent gestational trophoblastic disease treated with low-dose methotrexate: Efficacy, acute and long-term effects". *Br. J. Cancer,* 2003, *89,* 2197.

[36] Rustin G.J., Both M., Dent J., Salt S., Rustin F., Bagshawe K.D.: "Pregnancy after cytotoxic chemotherapy for gestational trophoblastic tumours". *Br. Med. J.,* 1984, *288,* 103.

[37] Berkowitz R.S., Goldstein D.P.: "Gestational trophoblastic disease". In: Ryan K., Berkowitz R.S., Barbieri R. (eds): "Kistner's Gynecology-Principles and Practice". St. Louiss, Mosby, 1995, 377.

[38] Yingna S., Yang X., Xiuyu Y., Hongzhao S.: "Clinical characteristics and treatment of gestational trophoblastic tumor with vaginal metastasis". *Gynecol. Oncol.,* 2002, *84*, 416.

[39] Garner E.I., Chang-Lee W.Y., Lu K.H., Goldstein D.P., Berkowitz R.S.: "Trophoblastic pulmonary embolization after hysterectomy for invasive complete mole. A case report". *J. Reprod. Med.*, 1999, *44,* 908.

[40] Garrett A.P., Garner E.O., Goldstein D.P., Berkowitz R.S.: "Methotrexate infusion and folinic acid as primary therapy for nonmetastatic and low-risk metastatic gestational trophoblastic tumors. 15 years of experience". *J. Reprod. Med.,* 2002, *47,* 355.

[41] Berkowitz R.S., Bernstein N.R., Laborde O., Goldstein D.P.: "Subsequent pregnancy experience in patients with gestational trophoblastic disease-New England Trophoblastic Disease Center, 1965-1992". *J. Reprod. Med.*, 1994, *39,* 228.

[42] Goldstein D.P., Berkowitz R.S.: "Staging system for gestational trophoblastic tumors". *J. Reprod. Med.,* 1984, *29*, 792.

Address reprint requests to:
A. HONIG, M.D.
Department of Obstetrics
and Gynecology
University of Wuerzburg
Joesef-Schneider Str. 4
97080 Wuerzburg (Germany)