Curr. Treat. Options in Oncol. (2017) 18: 58
DOI 10.1007/s11864-017-0502-0

Gynecologic Cancers (LA Cantrell, Section Editor)

Fertility Sparing Strategies in Patients Affected by Placental Site Trophoblastic Tumor

Benito Chiofalo, MD[1]
Vittorio Palmara, MD[1]
Antonio Simone Laganà, MD[1]
Onofrio Triolo, MD[1]
Salvatore Giovanni Vitale, MD[1]
Francesca Conway, MD[2]
Giuseppe Santoro, MD[3,4,*]

Address
[1]Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy
[2]Department of Biomedicine and Prevention, Section of Gynecology and Obstetrics, University of Rome Tor Vergata, Rome, Italy
[3]Department of Biomedical and Dental Sciences and Morpho-Functional Images, University of Messina, 1st floor Biologic Tower, Messina, Italy
[*,4]Department of Biomedical and Dental Sciences and Morpho-Functional Images, A.O.U. Policlinic "G. Martino", 1st floor Biologic Tower, Via Consolare Valeria, 98125, Messina, Italy
Email: giuseppe.santoro@unime.it

Published online: 24 August 2017

This article is part of the Topical Collection on *Gynecologic Cancers*

Keywords Gestational trophoblastic disease · Placental site trophoblastic tumor · Fertility sparing treatment · Intermediate trophoblast

Opinion statement

Placental site trophoblastic tumor (PSTT) is the least common and the most ambiguous gestational trophoblastic tumor. Presentation of PSTT may occur in the course of gestation or from 1 week to 14 years after a normal or an abnormal pregnancy (mole, ectopic pregnancy, abortion). The indicators of aggressive behavior for this tumor are not well established. Due to the rarity of this disease that usually affects women of childbearing potential, we aimed to review the current literature, to identify risk factors and the best conservative therapeutic choices among the cases described. We performed a systematic literature search of articles in English language, published from 1996 to 2017 and indexed in PubMed and Scopus. Based on

selective inclusion/exclusion criteria, we considered eight papers eligible for the review. Five were case reports and three were retrospective studies. We extracted and organized data into three different categories depending on the main treatment used. A total of 12 cases were treated with laparotomy; in 5 cases, the treatment was not curative. Therefore, a total abdominal hysterectomy was needed. Five cases were treated successfully with a minimally invasive approach, 2 with uterine evacuation, 2 with hysteroscopic resection, and 1 with a combined hysteroscopic/laparoscopic resection. Only 1 case treated with exclusive chemotherapy proved curative for the patient. Preservation of fertility in PSTT patients of childbearing age should be considered and as showed by the abovementioned studies, is a possible and safe therapeutic choice. Laparotomy for local uterine resection with the modified Strassman approach could be offered in patients at clinical stage 1 that are very motivated to retain fertility, extensively informing the patient of the risks and benefits related to this choice.

Introduction

Gestational trophoblastic diseases (GTDs) are a rare group of diseases originating from placental tissues that occur in women of childbearing age. Many different diseases are included in this group: partial and complete hydatidiform mole, invasive and metastatic mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor. Among GTDs, PSTT is the least common and the most ambiguous, usually manifesting a benign behavior, although it actually is a malignant disease with a possibly fatal outcome and a high chemo-resistance. Presentation of PSTT may occur in the course of gestation or from 1 week to years after a normal or an abnormal pregnancy (mole, ectopic pregnancy, abortion) [1, 2]. PSTT consists of intermediate trophoblast cells, which are a distinct portion of the trophoblasts, predominantly found at the normal placental implantation site and arising from the cytotrophoblasts [3]. Normally, the first symptom is abnormal vaginal bleeding, followed by amenorrhea, but the onset of the disease can also occur with nephrotic syndrome and/or uterine perforation [4••]. Metastasis can occur many years after diagnosis and have been reported in the lung, liver, lymph nodes, and brain [4••]; only 10% of cases are metastatic at the time of the diagnosis [5]. The indicators of aggressive behavior for this tumor are not well established. The most important prognostic factors taken into account are usually the number of mitosis [6, 7], the clinical stage, maternal age over 35 years, human chorionic gonadotropin (hCG) levels, a long (> 24 months) interval between the last pregnancy, and the clinical presentation of the disease [8]. For the diagnosis of this rare tumor, a combination of serum marker concentration and diagnostic imaging is necessary. Usually, hCG serum levels are not as high as in other GTDs given to the lack of syncytiotrophoblast, whereas human placental lactogen (hPL) may be elevated, as it is produced by the intermediate trophoblasts [9]. Ultrasonographic features show a large variability: in most of the cases, a solid mass is reported, with or without cystic areas [10–12]. Magnetic resonance imaging (MRI) is often used to confirm ultrasonographic findings and to identify potential extrauterine invasion, although CT can reveal the presence of distant metastasis. For uterine-confined disease, the safest therapeutic option is hysterectomy and pelvic lymph node sampling, followed by adjuvant chemotherapy. Nevertheless, for women of reproductive age, a conservative approach is often desired, but the risk of disease recurrence must be shared [13]. Due to the rarity of this disease, it is difficult to ascertain the risk of recurrence when a conservative approach is undertaken; therefore, we aimed to review the current literature, in order to identify risk factors and the best conservative management.

Materials and methods

We performed a systematic literature search of articles in English language, published from 1996 to 2017 and indexed in PubMed and Scopus. We searched

the following Medical Subject Headings (MeSH): "Placental Site Trophoblastic tumor" and "Fertility Sparing Treatment."

The initial database screening was performed by three authors (O.T., V.P., and F.C.), who were blinded to the aim of the study. Subsequently, other four authors (B.C, A.S.L., S.G.V., and G. S.) selected relevant information from the screened literature. We considered all original manuscripts (randomized, observational, and retrospective studies), case series, and case reports eligible. Furthermore, we extracted relevant information from the selected reviews.

Results

From our research, we considered nine papers eligible for the review [14–22]. Six were case reports [14, 15, 17, 18, 21, 22] and three were retrospective studies [16, 19, 20]. We extracted and organized data into three categories depending on the treatment used. All the data extracted from selected articles are summarized in Table 1.

Laparotomy

Laparotomy was the most commonly performed treatment in the reviewed studies to excise tumor with free myometrial margins and subsequent reconstruction of the uterine wall. Leiserowitz et al. [14] reported the first case of PSTT treated conservatively. The patient was 25 years old at diagnosis and presented irregular menstruation during breastfeeding of her child born 15 days earlier; serum levels of β-hCG and hPL were not particularly elevated (21 IU/L and 0.6 μg/mL, respectively). During surgery, a PSTT of 2 cm in diameter was removed from the anterior uterine wall. The patient had no recurrence in 4 years of follow-up.

Tsuju et al. [15] described a case of PSTT in a 26-year-old patient. She had spotting for 3 weeks and an episode of metrorrhagia after a spontaneous abortion occurred 4 months previously. Serum levels of β-hCG and hPL were 0.95 ng/mL and 0.37 μg/mL, respectively. Ultrasound and MRI showed a 3-cm uterine mass that was treated with two cycles of EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) chemotherapy and resection of the tumor. After 9 months, there was no evidence of disease (NED).

Machtinger et al. [16] reviewed their case series of PSTTs, in order to analyze clinical features. Among the 5 reported cases, only two were treated with a fertility sparing approach. One patient underwent excision of the tumor in a referring hospital; however, histological analysis showed invasion of vascular spaces, positive margins, and necrotic areas. After 6 weeks, computed tomography (CT) scan showed a suspicious uterine lesion; therefore, a total hysterectomy was recommended, although no residual tumor was found on the definitive specimen. After a follow-up of 33 months, the patient was alive with no evidence of recurrence.

Pfeffer et al. [17] published a case report of a 30-year-old woman with vaginal bleeding, following a complete molar pregnancy at 11 weeks gestation, treated with uterine evacuation. Because of the persistent elevated β-hCG serum levels and an ultrasound finding of a vascular solid lesion of the uterus, the patient underwent two chemotherapy lines: first line consisted of intramuscular methotrexate (50 mg on days 1, 3, 5, and 7) alternating with oral folinic acid (15 mg on days 2, 4, 6, and 8) repeated for 2 weeks; afterwards, she underwent combination

Table 1. Summary of relevant information from selected studies

Authors, year	Type of study	Age	Previous pregnancy	Pregnancy interval (months)	Mitotic count (per 10 HPF)	Treatment	Follow-up (months)
Leiserowitz et al. 1996 [14]	Case report	25	Term	15	1	Laparotomic TR	53 NED, 2 miscarriage, and 1 normal pregnancy
Tsuji et al. 2002 [15]	Case report	28	Term	4	2	Laparotomic TR	9 NED
Machtinger et al. 2005 [16]	Retrospective	29	In progress blighted ovum	–	8	Laparotomic TR	Hysterectomy after 6 weeks for a suspected recurrence; 33 NED
		26	Term	4	17	Hysteroscopic TR + sCT	29 NED
Pfeffer et al. 2007 [17]	Case report	30	Hydatidiform mole	NS	5–7	Laparotomic TR + sCT	Hysterectomy after 3 months for increased hCG levels; 29 NED
Liska et al. 2009 [18]	Case report	29	In progress twin pregnancy	–	1	Local resection during cesarean section	30 NED
Saso et al. 2011 [19]	Retrospective	37	Abortion	24	NS	MSP	Hysterectomy for close margins
		21	Tubal pregnancy	NS	NS	MSP	Hysterectomy for uncertain margins
		27	Term	24	NS	MSP	Hysterectomy for close margins
		36	Nulliparous	–	NS	MSP	12 NED
Shen et al. 2012 [20]	Retrospective	31	Term	1	Low	Laparotomic TR + sCT	34 NED
		28	Term	3	Low	D&C + sCT + iaCT	40 NED
		29	Abortion	3	Low	D&C + hysteroscopic TR + sCT + iaCT	45 NED
		27	Term	3	Low	D&C + sCT + iaCT	104 NED
		26	Abortion	4	Low	D&C + laparotomic TR + sCT + ia CT	49 NED (normal pregnancy)
		24	Hydatidiform mole	13	Low	D&C + laparoscopic and hysteroscopic TR + sCT + iaCT	10 NED

Table 1. (Continued)

Authors, year	Type of study	Age	Previous pregnancy	Pregnancy interval (months)	Mitotic count (per 10 HPF)	Treatment	Follow-up (months)
Ashton et al. 2014 [21]	Case report	24	Term	30	3/10	sCT + laparoscopic guided hysteroscopic resection	8 NED
Numnum et al. 2006 [22]	Case report	29	Abortion	3.5	NS	sCT	24 NED; normal singleton pregnancy after 24 months

HPF high-power fields, *NS* not specified, *sCT* systemic chemotherapy, *iaCT* intrauterine arterial infusion chemotherapy, *TR* tumor resection, *D&C* dilatation and curettage, *NED* no evidence of disease, *MSP* modified Strassman procedure

chemotherapy with etoposide, methotrexate, and dactinomycin, alternating weekly with cyclophosphamide and vincristine. Despite chemotherapy, the uterine lesion of 2.5 cm persisted on positron emission tomography (PET), but considering the desire of the patient to maintain her fertility, a third-line chemotherapy was administered (gemcitabine twice a week and carboplatin AUC5 every 3 weeks). Despite these therapies, the tumor size increased to 3.5 cm; therefore, the patient underwent resection of the right uterine fundus and pelvic lymph node sampling. The surgical specimen revealed a 2-cm PSTT with negative margins and 5–7 mitotic count per 10 high-power field (HPF). During the adjuvant therapy with paclitaxel and etoposide alternating every 2 weeks with paclitaxel and cisplatin, β-hCG increased once again, despite negative MRI and CT/PET. For this reason, total abdominal hysterectomy with right salpingo-oophorectomy was performed, and the histological analysis found a microscopic aggregate of PSTT. After 2.5 years, the patient was alive with NED.

Liszka et al. [18] resected an intrauterine lesion during a cesarean section for a spontaneous twin pregnancy in a 29-year-old woman. Histological analysis found a 4 × 3 × 3-cm PSTT with a low mitotic index and negative margins. No adjuvant therapies were administrated. After 30 months of follow-up, the patients had NED.

Saso et al. [19] described a case series of four PSSTs and one epithelioid trophoblastic tumor treated with a modified Strassman procedure, consisting of a temporary devascularization of the uterus with a full thickness excision of the uterine lesion with 1 cm of free margins. Due to positive or unclear margins, in 4 cases, a total abdominal hysterectomy was performed. The only successful conservative treatment was performed in a 36-year-old nulliparous woman: at the last follow-up 1 year later, the patient had NED and her menstrual cycle was normal.

Shen et al. [20] described retrospectively the first case series of PSTTs successfully treated with conservative approaches. They described six patients with a mean age of 27.5 years. Two of these patients with a nodular lesion were treated with a laparotomy for tumor resection followed by systemic chemotherapy; the second also received intrauterine arterial chemotherapy. The intrauterine arterial chemotherapy regimen was floxuridine-based and was infused 8 h per day in 5 consecutive days of treatment. Both the patients were alive with NED after a mean follow-up of 41.5 months, and a successful spontaneous pregnancy was described in the second patient 22 months after treatment.

Minimally invasive treatments

The second case described by Macthinger et al. [17] occurred with vaginal bleeding and β-hCG levels 175 IU/L, 4 months after vaginal delivery. A 20×20-mm intrauterine mass was effectively treated with a hysteroscopic resection followed by three courses of EMA-CO. The patient was alive without evidence of disease 29 months after surgery.

Four patients described by Shen et al. [20] (three with a polypoid lesion and one with a nodular lesion) were treated with uterine evacuation, one case also with hysteroscopic resection, and another with combined hysteroscopic and laparoscopic resection. All of these patients received intrauterine arterial and systemic chemotherapy. All the patients were alive and free of disease with a mean follow-up of 49.75 months. Two of these patients were not planning a pregnancy yet, the patient that received hysteroscopic treatment failed to achieve pregnancy and underwent infertility management, and the last patient, treated

with a combined laparotomic and hysteroscopic approach, opted for contraceptive therapy in consideration of a short interval since the disease (10 months).

Similarly, a recent case reported by Ashton et al. [21] occurred in a 28-year-old patient, with a history of uncomplicated term vaginal delivery, 2.5 years prior to presentation of the disease with irregular vaginal bleeding. Laboratory values revealed a serum hCG of 17 mIU and normal serum hPL. MRI of the pelvis showed a small fundal lesion with no evidence of myometrial invasion. Since the patient refused hysterectomy and lymph node sampling, she underwent a laparoscopic-guided hysteroscopic resection of the tumor. Nevertheless, the pathology of the resected specimen showed extensive myometrial invasion with residual PSTT and, for this reason, the patient ultimately agreed to hysterectomy with pelvic lymph node sampling and adjuvant treatment with paclitaxel, cisplatin alternating with paclitaxel, etoposide (TP/TE). Three months after the surgery, β-hCG was below 5 mIU/mL and CT scan was negative.

Pharmacologic treatment only

The only case successfully treated with medical treatment exclusively was described by Numnum et al. [22]. They reported a case report of a 29-year-old nulliparous woman with vaginal bleeding and elevated β-hCG (130 IU/L), without radiological signs of disease, in which a diagnostic uterine curettage diagnosed PSTT. The patient was treated with a chemotherapy regimen consisting of etoposide, methotrexate, and actinomycin D on day 1 followed by etoposide and cisplatin on day 8 (EMA-EP). The patient responded well to the treatment and her hCG decreased from 130 IU/L to < 5 IU/L after three cycles of EMA-EP. She received three additional cycles after her hCG was < 5 IU/L. Two years after completion of the therapies, she was free of disease and had a successful singleton pregnancy.

Considerations

Based on our literature search, we identified 18 cases of PSTT treated with a fertility sparing approach [14–22]. Eleven patients underwent first-line open surgery that was effective in 6 cases [14, 15, 18–20]; in the remaining 5 cases, a total hysterectomy was necessary for suspected relapse or close/positive margins in the post-operative specimen [16, 17, 19].

Minimally invasive techniques are reported mostly for polypoid tumors, treated with operative hysteroscopy [16, 17, 21]. Laparoscopy was utilized in 2 cases in association with hysteroscopy [20, 21]. Only one patient was treated with exclusive chemotherapy [22].

Some authors used post-operative chemotherapy [16, 17, 21]; in other cases, systemic and intrauterine arterial chemotherapy were administrated preoperatively [20]; lastly in some cases, neither adjuvant nor neoadjuvant therapy were given [14–16, 18, 19].

Conclusion

Preservation of fertility in PSTT patients of reproductive age is a reasonable therapeutic option. Based on our review of the available literature, conservative treatments were effective in 72% of cases. However, because of the lack of well-

defined prognostic factors and of the relative chemo-resistance of this disease, the current evidence does not allow to draw firm conclusions regarding the gold standard management for patients affected by PSTT who desire to preserve fertility [23].

As we recently highlighted [4••], each patient should be considered individually. Multidisciplinary assessment is necessary to evaluate risk factors, such as the mitotic count, ß-hCG level, the interval since the previous pregnancy, the stage of disease, the age of the patient, and desire to maintain fertility in order to propose a tailored treatment. According to a PSTT series from the UK, the most important prognostic factor identified on a multivariate analysis is the interval between the antecedent pregnancy and the clinical presentation of the disease, regardless of disease stage or ß-hCG levels [8]. Local uterine resection via laparotomy with the modified Strassman approach could be offered to patients with clinical stage-one disease who are motivated to retain fertility, informing the patient of risks and benefits related with this choice. Our analysis showed that minimally invasive approaches could be considered a feasible option in cases of polypoid intrauterine tumor.

In any case, revision surgery for a radical treatment is advised in case of positive or unclear margins and multifocal disease. In patients treated with chemotherapy, ovarian function may be affected, especially when multiple agents are administered; therefore, ovarian tissue cryopreservation is advised [24]. Larger cohorts and long-term follow-up are necessary to identify the best fertility sparing therapeutic approach for PSTT patients.

Compliance with Ethical Standards

Conflict of Interest

Benito Chiofalo, Vittorio Palmara, Antonio Simone Laganà, Onofrio Triolo, Salvatore Giovanni Vitale, Francesca Conway, and Giuseppe Santoro declare they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

1. Kurman RJ. The morphology, biology and pathology of intermediate trophoblast: a look back to the present (review). Hum Pathol. 1991;22:847–55.
2. Lan C, Li Y, He J, Liu J. Placental site trophoblastic tumor: lymphatic spread and possible target markers. Gynecol Oncol. 2010;116(3):430–7.
3. Shih IM, Kurman RJ. The pathology of intermediate trophoblastic tumors and tumor-like lesions. Int J Gynecol Pathol. 2001;20(1):31–47.
4.•• Santoro G, Laganà AS, Micali A, Barresi V, Giacobbe V, Palmara V. Historical, morphological and clinical overview of placental site trophoblastic tumors: from bench to bedside. Arch Gynecol Obstet. 2017;295(1):173–87.

The number of cases described in literature was updated, and a model (PSTT model) that collects and unifies PSTT evidences as this would be useful to identify worldwide precise prognostic factors (which are still lacking) was suggested.

5. Dessau R, Rustin GJS, Dent J, Paradinas FJ, Bagshawe KD. Surgery and chemotherapy in the management of placental site tumor. Gynecol Oncol. 1990;39:56–9.
6. Scully RE, Young RH. Trophoblastic pseudotumor: a reappraisal. Am J Surg Pathol. 1981;5(1):75–6.
7. Finkler NJ. Placental site trophoblastic tumor. Diagnosis, clinical behavior and treatment. J Reprod Med. 1991;36(1):27–30.
8. Schmid P, Nagai Y, Agarwal R, Hancock B, Savage PM, Sebire NJ, et al. Prognostic markers and long-term outcome of placental-site trophoblastic tumours: a retrospective observational study. Lancet. 2009;374(9683):48–55.
9. Kurman RJ, Young RH, Norris HJ. Immunocytochemical localization of placental lactogen and chorionic gonadotropin in the normal placenta and trophoblastic tumors, with emphasis on intermediate trophoblast and the placental site trophoblastic tumor. Int J Gynecol Pathol. 1984;3:101–21.
10. Sakamoto C, Oikawa K, Kashimura M, Egashira K. Sonographic appearance of placental site trophoblastic tumor. J Ultrasound Med. 1990;9:533–5.
11. Caspi B, Elchalal U, Dgani R, Ben-Hur H, Rozenman D, Nissim F. Invasive mole and placental site trophoblastic tumor. Two entities of gestational trophoblastic disease with a common ultrasonographic appearance. J Ultrasound Med. 1991;10(9):517–9.
12. Abulafia O, Sherer DM, Fultz PJ, Sternberg LB, Angel C. Unusual endovaginal ultrasonography and magnetic resonance imaging of placental site trophoblastic tumor. Am J Obstet Gynecol. 1994;170(3):750–2.
13. Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C, et al. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi39–50.
14. Leiserowitz GS, Webb MJ. Treatment of placental site trophoblastic tumor with hysterotomy and uterine reconstruction. Obstet Gynecol. 1996;88(4 Pt 2):696–9.
15. Tsuji Y, Tsubamoto H, Hori M, Ogasawara T, Koyama K. Case of PSTT treated with chemotherapy followed by open uterine tumor resection to preserve fertility. Gynecol Oncol. 2002;87(3):303–7.
16. Machtinger R, Gotlieb WH, Korach J, Fridman E, Apter S, Goldenberg M, et al. Placental site trophoblastic tumor: outcome of five cases including fertility preserving management. Gynecol Oncol. 2005;96(1):56–61.
17. Pfeffer PE, Sebire N, Lindsay I, McIndoe A, Lim A, Seckl MJ. Fertility-sparing partial hysterectomy for placental-site trophoblastic tumour. Lancet Oncol. 2007;8(8):744–6.
18. Liszka L, Wilk M, Wodolazski A, Palen P, Sikora J. Successful treatment of placental site trophoblastic tumor in twin pregnancy without hysterectomy. Tumori. 2009;95(1):108–11.
19. Saso S, Haddad J, Ellis P, Lindsay I, Sebire NJ, McIndoe A, Seckl MJ, Smith JR. Placental site trophoblastic tumours and the concept of fertility preservation. BJOG 2012;119(3):369–374; discussion 374.
20. Shen X, Xiang Y, Guo L, Feng F, Wan X, Xiao Y, et al. Fertility-preserving treatment in young patients with placental site trophoblastic tumors. Int J Gynecol Cancer. 2012;22(5):869–74.
21. Ashton E, Szutowska M, Shafer A, Hoffman J. Attempted conservative management of a placental site trophoblastic tumor: a case report. Conn Med. 2014;78(8):475–7.
22. Numnum TM, Kilgore LC, Conner MG, Straughn JM Jr. Fertility sparing therapy in a patient with placental site trophoblastic tumor: a case report. Gynecol Oncol. 2006;103(3):1141–3.
23. Tse KY, Ngan HY. Gestational trophoblastic disease. Best Pract Res Clin Obstet Gynaecol. 2012;26(3):357–70.
24. Jensen AK, Macklon KT, Fedder J, Ernst E, Humaidan P, Andersen CY. 86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children. J Assist Reprod Genet. 2017;34(3):325–36.