TREATMENT OF GESTATIONAL TROPHOBLASTIC DISEASES AT TAMPERE UNIVERSITY HOSPITAL BETWEEN YEARS 2002 AND 2013 – USED PROTOCOLS, RESULTS AND COMPLICATIONS

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KORTELAINEN LAURA: RASKAUTEEN LIITTYVIEN TROFOBLASTISAIRAUKSIEN HOITO TAMPEREEN YLIOPISTOLLISESSA SAIRAALASSA VUOSINA 2002–2013 – KÄYTETYT HOITOPROTOKOLLAT, HOIDON TULOKSET SEKÄ HOIDON KOMPLIKAATIOT (TREATMENT OF GESTATIONAL TROPHOBLASTIC DISEASES AT TAMPERE UNIVERSITY HOSPITAL BETWEEN YEARS 2002 AND 2013 – USED PROTOCOLS, RESULTS AND COMPLICATIONS)

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Lähtökohta: Raskauteen liittyvät trofoblastisairaudet, mukaan lukien rypäleraskaus, invasiivinen moola ja korionkarsinooma eli istukkasyöpä sekä istukkapedin trofoblastituumori, ovat monimutkaisia, hoitamattomana hengenvaarallisia tautitiloja. Aikaisempien tutkimusten mukaan pienten riskien taudeissa parantumisprosentti on nykyään lähes 100 % ja suurten riskin taudeissa 85–94 %. Tämän tutkimuksen tarkoituksena oli selvittää, vastaavatko Tampereen yliopistollisessa sairaalassa (TAYS) saavutetut hoitotulokset aikaisemmissa tutkimuksissa esitettyjä paranemisprosentteja.

Metodit: Tutkimus perustui vuosien 2002–2013 sairaskertomuksiin, joissa ICD–10 diagnoosinumerona oli käytetty yhtä tai useampaa seuraavista: rypäleraskaus (ICD–10: O01), invasiivinen moola (D39.2), korionkarsinooma (C58) tai istukkapedin trofoblastituumori (D39.2). Kun tutkimukseen soveltumattomat tapaukset, kuten ne, joissa oli käytetty väärää diagnoosinumeroa, poissuljettiin, aineisto koostui yhteensä 78 sairaskertomuksesta. Kerättäessä dataa trofoblastitautien jälkeisistä raskauksista, kaikki keräämishetkellä (syksy 2014) saatavilla oleva informaatio sisällytettiin mukaan.

Tulokset: 75,6 % tapauksista oli ei-neoplastisia raskaudenaikaisia trofoblastitauteja, kattaen 36 täydellistä rypäleraskautta ja 23 osittaista rypäleraskautta. Loput 24,4 % tapauksista oli neoplastisia trofoblastitauteja: 13 persistenttiä moolaa, 3 invasiivista moolaa ja 3 korionkarsinoomaa. Aineistoon ei sisältynyt yhtään istukkapedin trofoblastituumoria. Suurin osa hyvänlaatuisista tapauksista kaavittiin vain kerran (91,2 %) ja pahanlaatuisista tapauksista kerran kaavittiin 47,4 %. Huomattavasti suurempi määrä maligneja tapauksia (36,8 %) vaati toisen kaavinnan benigneihin tapauksiin verrattuna (8,8 %). Lisäksi yhden malignin tapauksen yhteydessä ei kaavintaa suoritettu kertaakaan, ja kahden malignin tapauksen yhteydessä kaavinta suoritettiin kolmesti. Suurimmalla osalla (67,3 %) benigneistä tapauksista hCG-arvot normalisoituivat ensimmäisen kahden kuukauden aikana kaavinnan jälkeen. Vastaavasti maligneissa tapauksissa suurimalla osalla (78,9 %) hCG-arvojen normalisoituminen tapahtui kahden ja neljän kuukauden välillä kaavinnan jälkeen. Ensisijainen hoito pienen riskin neoplastisille taudeille oli yksittäinen solusalpaajahoito, joko metotreksaatilla tai aktinomysiini D:llä toteutettuna. Suuren riskin taudit puolestaan hoidettiin ensisijaisesti yhdistelmäsolusalpaajahoidolla, EMA/CO:lla. Ensisijainen solusalpaaja vaihdettiin toiseen solusalpaajan yhteensä kuudesti, johtuen joko ensisijaisen solusalpaajan puutteellisesta tehosta tai sivuvaikutuksista. Solusalpaajiin kuvattiin liittyneen lukuisia erilaisia sivuvaikutuksia, jotka suurimmaksi osaksi vastasivat aikaisemmassa kirjallisuudessa kuvattuja lääkeainekohtaisia sivuvaikutuksia. Yhdistelmähoitoon (EMA/CO) liittyi lisäksi kolme vakavampaa haittavaikutusta. Yksi potilas kärsi ohimenevästä näön menetyksestä, jonka aiheutti metotreksaatti. Toisella potilaalla taas diagnosoitiin sekä syvä laskimotukos että akuutti leukemia. Molemmat potilaat kuitenkin toipuivat haittavaikutuksista, eikä pitkäaikaista haittaa jäänyt. Kaikki Tampereen yliopistollisessa sairaalassa hoidetut, raskauteen liittyvää trofoblastitautia sairastaneet potilaat paranivat eikä kuolemantapauksia esiintynyt yhtään. Lisäksi yhteensä noin 74 % hoidetuista potilaista on synnyttänyt trofoblastitaudin jälkeen tai oli raskaana dataa kerättäessä (syksy 2014).

Päätelmät: Kaikki TAYS:ssa vuosina 2002–2013 hoidetut, trofoblastitautia sairastaneet potilaat paranivat eikä trofoblastitaudeista tai niiden hoidosta jäänyt potilaille pitkäaikaishaittoja. Voidaan siis todeta, että TAYS:ssa saavutetut hoitotulokset vastaavat aikaisemmassa kirjallisuudessa esitettyjä paranemisprosentteja.

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1 ABSTRACT

Objective. Gestational trophoblastic diseases (GTD), including hydatidiform mole, invasive mole, choriocarcinoma and placental-site trophoblastic tumor, are complex diseases that can be fatal if not treated. According to previous studies, cure rates are nowadays excellent, approaching almost 100% with low-risk diseases and 85-94% with high-risk diseases. The purpose of this study was to determine whether cure rates achieved in treatment of GTDs in Tampere University Hospital (Tampereen Yliopistollinen Keskussairaala, TAYS later in this study) are similar to cure rates described in other studies.

Methods. The study was based on the medical records between years 2002 and 2013 that included an ICD-10 diagnosis number for hydatidiform mole (O01), invasive mole (D39.2), choriocarcinoma (C58) or placental-site tumor (D39.2). After excluding unsuitable cases, such as cases with wrong diagnosis number, the research data included 78 valid cases. When collecting data concerning successful pregnancies after gestational trophoblastic diseases, all data available until the collection date (autumn 2014) was included.

Results. 75.6% of the cases were non-neoplastic gestational trophoblastic diseases, including 36 complete moles and 23 partial moles. The rest, 24.4% of the cases, were neoplastic GTDs, including 13 persistent moles, 3 invasive moles and 3 choriocarcinomas. The data included no placental-site trophoblastic tumors. Majority of both benign (91.2%) and malignant cases (47.4%) were evacuated only once, but a notably larger amount of malignant cases (36.8%) needed two evacuations, compared to benign cases evacuated twice (8.8%). In addition, there was one neoplastic case that was not evacuated at all, and two cases where evacuation was performed three times. With the majority of the malignant cases (78.9%), it took two to four months after evacuation for the hCG level to normalize, whereas with about two-thirds of the benign cases, the hCG level normalized within two months after evacuation. The primary treatment for the low-risk neoplastic diseases was single-agent chemotherapy with either methotrexate or actinomycin D (dactinomycin), whereas high-risk cases were primarily treated with multidrug EMA/CO treatment. Six times the primary chemotherapy had to be replaced by alternative chemotherapy because of the side effects or inadequate efficiency. Most of the side effects of different chemotherapies found in TAYS were similar to the side effects described in other studies. In addition, three more severe complications occurred with patients treated with EMA/CO. One patient suffered from a transient loss of vision caused by methotrexate, and another one was diagnosed with both leukemia and phlebothrombosis. Fortunately, no long-term harm was caused by these. All the patients treated at TAYS got disease free, and no deaths occurred. Additionally, 74% of the patients have given birth after GTD, or were pregnant when the data was collected (autumn 2014).

Conclusion. All the patients treated at TAYS between years 2002 and 2013 were cured, and no long-term harm was caused by either the trophoblastic disease or its treatment. Based on the results of this study, it can be affirmed that cure rates achieved at TAYS are comparable to cure rates described in other studies.

2 INTRODUCTION

2.1 Definition of gestational trophoblastic diseases

Hydatidiform mole, invasive mole and choriocarcinoma are gestational trophoblastic diseases. Hydatidiform mole is a premalignant disorder and can be considered to be either complete or partial. Hydatidiform mole can become an invasive mole if it penetrates into the myometrium. Invasive mole can also metastasize especially to lungs and vagina. Choriocarcinoma can develop after molar pregnancy or any other pregnancy. Its characteristics include remarkable changes of placental tissue, and metastasizing to other organs. Both invasive mole and choriocarcinoma are considered to be malignant, neoplastic disorders. Malignant gestational trophoblastic diseases also include placental-site trophoblastic tumor and its variant, an epithelioid trophoblastic tumor. Both of these disorders are rare.(1, 2, 5, 6, 8) The term persistent mole, used in this study, stands for a hydatidiform mole that has not invaded into the myometrium, but its management requires chemotherapy and thus it is considered to be a neoplastic disorder as well.

2.2 Epidemiology and risk factors

The incidence of a gestational trophoblastic disease, both benign and malignant, varies within regions. Incidences in Europe (including Finland), North America, New Zealand and Australia are lower than incidences in Southeast Asia and Japan, for example. (2, 5, 6, 7, 8, 9) In Scandinavia, for example, in Norway and Sweden, the incidence of a hydatidiform mole is less than one per 1000 pregnancies (2) whereas in Japan and Southeast Asia, the incidence of a hydatidiform mole is 2–10 per 1000 pregnancies, depending on the source (2, 8). The incidence of choriocarcinoma in Europe and North America is approximately 1 per 40 000 pregnancies and in Southeast Asia and Japan higher at 9.2 per 40 000 pregnancies. However, the incidence rates of hydatidiform mole and choriocarcinoma have both declined in all populations over the past 30 years.(2)

Some risk factors for hydatidiform mole have been established. These are the extremes of maternal age (< 20 years old, > 40 years old) (2, 8, 9) and antecedent pregnancy being a molar pregnancy. The risk of molar pregnancy is also increased among women with history of miscarriages.(2, 8) Advanced maternal age and a prior complete hydatidiform mole are considered to be risk factors for choriocarcinoma. The risk of choriocarcinoma after a complete molar pregnancy is over a thousand times greater than with other pregnancies.(8)

2.3 Pathogenesis

A surplus of chromosomes inherited from father is typical for a hydatidiform mole. The development of a complete hydatidiform mole usually requires an ovum without maternal chromosomes that is fertilized by sperm with duplicated genome, hence producing androgenetic karyotype 46XX. In some rare cases, a complete hydatidiform mole is developed by two sperms fertilizing an empty ovum, in which case karyotype can be either 46XY or 46XX. A partial hydatidiform mole usually arises when a seemingly healthy ovum is fertilized by two sperms, producing a triploid karyotype.(5) Absence of fetus or embryo and diffuse swelling of villi and trophoblastic hyperplasia are typical pathological features for a complete hydatidiform mole (8). In a partial mole, a fetus/embryo is developed but it is abnormal and therefore inviable (6, 8). In addition, in partial mole swelling of villi and trophoblastic hyperplasia is focal. 15–20% of complete hydatidiform moles and 5% of partial moles develop into some neoplastic trophoblastic disorder (invasive mole or choriocarcinoma).(8)

When a hydatidiform mole penetrates into the myometrium, a malignant invasive mole has developed. Swollen villi and hyperplasia of trophoblasts are typical pathological features of an invasive mole (2,8). Approximately 15% of invasive moles metastasize to vagina or lungs. Typical for an invasive mole is that the diagnosis is usually clinical instead of pathological and treatment can be started without a histopathological analysis.(8)

Hyperplasia and anaplasia of syncytiotrophoblasts and cytotrophoblasts, absence of villi, hemorrhage and necrosis are pathological characteristics for a choriocarcinoma (4, 8). Choriocarcinoma penetrates rapidly trough the myometrium, and metastasizes to other organs, such as lungs, liver, brain and vagina. Choriocarcinoma is more common after molar pregnancy than other pregnancies, such as term or preterm gestation or tubal pregnancy.(8) Approximately 2–3% of hydatidiform moles develop into choriocarcinoma (8, 9).

A placental-site tumor and its variant, an epithelioid trophoblastic tumor are both very rare trophoblastic diseases (8). Whereas hydatidiform mole and choriocarcinoma originate from villous trophoblasts, a placental-site tumor arises from interstitial trophoblast (5). A placental-site trophoblastic tumor can develop after any type of pregnancy. Comparing to choriocarcinoma, a placental-site tumor arises more slowly, metastasizes later and produces less hCG, and unlike choriocarcinoma, primary management of placental-site tumor is surgical.(5)

2.4 Clinical presentation

The most common symptom of a complete hydatidiform mole is vaginal bleeding. Other typical symptoms are the too large size of the uterus in relation to pregnancy weeks and hyperemesis. Pregnancy induced

hypertension can also be one of the symptoms, but nowadays it is rare because molar pregnancies are typically diagnosed earlier. In addition, bilateral enlarged theca lutein cysts of the ovaries are occasionally present. Vaginal bleeding is characteristic also for a partial hydatidiform mole.(8) The size of the uterus is usually normal or too small in relation to pregnancy weeks, and symptoms are similar to missed or incomplete abortion (2, 6, 8). Other, quite rare symptoms of a hydatidiform mole are hyperthyroidism, anemia, and toxemia of pregnancy (6). The symptoms mainly result from an elevated hCG level, which is usually higher in a complete hydatidiform mole (over 100 000 IU/l) than in a partial mole (under 100 000 IU/l) (4, 6, 8).

Malignant disorders may have varying clinical presentations depending on the type of the pregnancy preceding the malignancy and the extent of disorder (8). Vaginal bleeding is a common symptom, especially when antecedent pregnancy has been a molar pregnancy (2, 8). Postmolar neoplasm should be suspected if after evacuation of a molar pregnancy, the uterus is too large, or if irregular bleeding or bilateral ovarian enlargement exists (4, 6). The patient may also suffer from stomach pains (2). Other symptoms can be, for example, cough, hemoptysis and dyspnea caused by lung metastasis or headache, hemiplegia or seizures caused by brain metastasis (2, 8). Uterine bleeding and subinvolution are symptoms of postpartum choriocarcinoma (8).

2.5 Diagnosis

When diagnosing gestational trophoblastic diseases, the two most important examinations are pelvic ultrasonography and quantitative measurement of human chorionic gonadotropin (hCG) in serum and, if necessary, in urine (2, 4, 5, 6, 8). Characteristic findings for a complete hydatidiform mole are high concentration of hCG in serum, and so-called snowstorm image seen in pelvic ultrasonography (2, 5, 6), which is caused by heterogenic mass filling uterine cavity (5, 6). Typically, no fetus can be found. When it comes to the partial mole, cystic focal changes and typically abnormal fetus can be seen in ultrasonography.(6, 8) The hCG level in a partial mole is usually not as elevated as in a complete mole (8).

Postmolar gestational trophoblastic neoplasia can be diagnosed by elevating or plateauing concentrations of hCG after evacuation of hydatidiform mole. Non-molar choriocarcinomas are also usually diagnosed by an elevated hCG level. Discovery of metastasis is also an important part of choriocarcinoma's diagnostics whether it is post- or non-molar.(8) In differential diagnosis of trophoblastic diseases, the ratio between the concentrations of free-β-hCG and total hCG can be used. If the ratio is above 5%, the disorder can be considered to be choriocarcinoma.(2, 7) Certain radiological studies are a part of the diagnosis of gestational trophoblastic neoplasia. To rule out lung metastasis, a chest x-ray and, in some cases, a CT-scan of the chest should be performed. Brain metastasis can be ruled out by either CT-scan or MRI-scan of the brain and for abdominal metastasis, abdominal CT-scan is put into practice.(1, 2, 5)

2.6 Classification of malignant trophoblastic diseases

When classifying trophoblastic neoplasia and estimating their risk, two criteria can be used. The International Federation of Gynecology and Obstetrics (FIGO) has defined a staging criteria for gestational trophoblastic neoplasia. It has four stages from I to IV, which describe the anatomic distribution of the disorder (table 1). Another classification criteria used is a risk factor scoring system created by World Health Organization (WHO). It is a system where risk factors like mother's age, antecedent pregnancy and pretreatment hCG are rated with score from 0 to 4 (0, 1, 2, 4). The more significant the risk factor, the higher the score. Individual scores are then added together and if the total score is under 7, the disorder is considered to be low risk, but if the total score is 7 or above, the disorder is considered to be high-risk (Table 2).(1, 2, 5, 6)

Table 1: FIGO staging criteria (1)

FIGO staging criteria	Explanation
Stage I	Disease that has confined to the uterus
Stage II	Disease that has extended out of the uterus, but is limited to genital structures
Stage III	Disease that has metastasized to the lungs
Stage IV	Disease that has metastasized to any other sites

2.7 Treatment

Hydatidiform moles, both partial and complete, are primarily treated with suction curettage, which allows patients to maintain their fertility. Another option for treatment is hysterectomy, if fertility is not wished to be maintained.(2, 8) Because of residual tissue sometimes left behind, occasionally suction curettage needs to be performed twice or rarely even more times.

Primary treatment for gestational trophoblastic neoplasia is chemotherapy. Choosing the treatment is based on classifying the disorders by their stage and risk-factor score (FIGO, WHO) to either a low- or high-risk disease. Low-risk diseases are primarily treated with single-agent chemotherapy, whereas high-risk diseases are treated with multidrug therapy.(1, 2, 3, 5) (Table 2)

A low-risk disease is a disease that has confined to uterus (stage I), or a disease that has extended to genitals or metastasized to lungs (stage II or III), but has a total risk-factor score under 7 (WHO) (Table 2). Low-risk

diseases are managed with monochemotherapy, using either methotrexate or actinomycin D (dactinomycin).(1, 3) Because actinomycin D has more toxic side effect profile than methotrexate, it is usually the secondary option after methotrexate (1). There are several different protocols for methotrexate therapy, with varying doses, schedules and routes of administration. One of the most used protocols is methotrexate 0,4 mg/kg (maximum 25 mg) IV or IM given daily for five days every other week. Another used protocol is to give a higher dose of methotrexate (1 mg/kg/d, IM) every other day (days 1, 3, 5, 7) and to give folinic acid (0.1 mg/kg/d) on days 2, 4, 6 and 8 with at least one week separating the courses.(1, 2) If the used chemotherapy is actinomycin D, the protocol is to give 10–13 µg/kg/d (IV) for 5 days every other week (1).

With all the protocols, cycles of chemotherapy are continued until the hCG values have returned to normal, and at least one cycle is given after that. With single-agent chemotherapy, cure rates for low-risk diseases approach 100%. Sometimes, a low-risk disease does not respond to single-agent chemotherapy as wished. An alternative single-agent therapy is started if the hCG level plateaus above normal, or if toxicity makes it impossible to use adequate doses or frequency. A multidrug therapy is started if the hCG level rises significantly, if new metastasis appear, or if a resistance to single-agent chemotherapy has developed.(1)

A high-risk disease is a disease that has metastasized to genitals or to lungs (stages II or III) with a total risk-factor score of 7 or above, or a disease that has metastasized to any other site (stage IV) (Table 2). High-risk diseases are primarily treated with multidrug chemotherapy. Nowadays, the most commonly used combination is called EMA/CO, which consists of etoposide, methotrexate (with folinic acid), actinomycin D, cyclophosphamide and vincristine.(1, 2, 3) EMA/CO was introduced in the 1980's, and it has resulted in improved long-term survival rates in high-risk cases, nowadays being 85–94%.(1, 2, 3, 7) EMA/CO schedule is the following: On day number one patient receives etoposide (100 mg/m^2 IV), actinomycin D (0.5 mg IV) and methotrexate (300 mg/m^2 IV for 12 h), on day number two patient is given etoposide (100 mg/m^2 IV), actinomycin D (0,5 mg IV) and folinic acid (15 mg PO/IM for 12 h, 4 doses), and on day number eight patient receives cyclophosphamide (600 mg/m^2 IV) and vincristine (1 mg/m^2 IV). This cycle is repeated every other week. These cycles are continued until the hCG level has normalized, and 2–3 times after that. Metastasis can be simultaneously treated with irradiation or surgery, depending on their location. If the disease does not respond to EMA/CO as hoped, other types of multidrug combinations can be used.(1)

Table 2: Classification and treatment of trophoblastic neoplasia (1)

	Stage (FIGO)	Risk factor score (WHO)	Chemotherapy
Low risk	I	-	Single-agent therapy (methotrexate or actinomycin D)
	II or III	< 7	
High risk	II or III	≥ 7	Multidrug therapy (EMA/CO)
	IV	-	

Most common side effects of methotrexate are stomatitis (1), mucositis, myelosuppression, rise of aminotransferase levels, and pleural pain (2). Alopecia and nausea are not common side effects (1, 3). As mentioned earlier, actinomycin D has more toxic side effect profile than methotrexate, and it is often associated with alopecia, nausea (1, 3, 4) and vomiting (4). It can also cause local tissue damage if IV extravasation occurs (1, 3). EMA/CO's side effects are nausea, hair loss and myelosuppression (2) because of the usage of both methotrexate and actinomycin D. Neither methotrexate, actinomycin D nor EMA/CO affects patient's fertility (1, 2, 5) and they do not increase the incidence of congenital malformations in subsequent pregnancies (5).

2.8 Follow-up

After evacuation of a hydatidiform mole, serum hCG level is regularly measured to see whether the concentration reduces fast enough. This enables detecting trophoblastic sequelae, invasive mole or choriocarcinoma, as early as possible. In addition to measuring hCG level in serum, clinical findings, such as the size of the uterus and cessation of the bleeding after evacuation, should be considered when estimating the healing process of a hydatidiform mole.(8)

After a low-risk trophoblastic disease, regular measurements of serum hCG level continue for 12 months after the hCG value has normalized, so that possible relapse of the disorder can be noticed as soon as possible (1). The hCG level also needs to be regularly checked after a high-risk disease. In Finland, the follow-up of high-risk diseases treated with multidrug therapy lasts five years altogether.(2)

In addition to measuring the hCG level regularly, physical examinations should be performed in intervals of 6–12 months during the follow-up after the trophoblastic neoplasia. Contraception, preferably oral substances, should be started during the treatment and maintained at least one year after the completion of the chemotherapy. Additionally, pelvic ultrasound should be performed in the first trimester of subsequent

pregnancy, to confirm a normal gestation. The placentas from subsequent pregnancies should be examined histopathologically, and serum hCG level measured six weeks after any pregnancy.(1)

3 METHODS

This study is a retrospective cohort study based on medical records of gestational trophoblastic diseases treated at Tampere University Hospital between years 2002 and 2013. Medical records were selected based on ICD–10 diagnosis number, so that eventually all cases of hydatidiform moles (O01), invasive moles (D39.2), choriocarcinomas (C58) and placental-site trophoblastic tumors (D39.2) were included. When collecting data concerning successful pregnancies after gestational trophoblastic diseases, all data available until the collection date (autumn 2014) was included.

Medical records were analyzed and information regarding the mother, the current gestational trophoblastic disease, the treatment of the GTD and the healing process was collected (Table 3).

Table 3: Information gathered from the medical records

Information gathered from the medical records	
Mother	Age
	Pevious gestations
	Previous parturitions
Current trophoblastic disease (hCG)	Pre- and post-treatment hCG-values
	Time it took for the hCG level to normalize
Current trophoblastic disease (treatment)	Number of evacuations needed
	Type of chemotherapy used
	Additional treatments (surgery) used
Current trophoblastic disease (complications)	Side effects and complications
Subsequent pregnancies	Relapse of gestational trophoblastic disease
	Following pregnancies (normal/abnormal, successful or not)

Some of the medical records were invalid and therefore excluded from the data. Reasons for invalidity were, for instance, incorrect use of GTD diagnosis numbers (ICD–10) for other disorders invalid for this study, and for suspicions of molar pregnancies, which turned out to be non-molar. In addition, total of three cases were ruled out because of inadequate information. These cases were consultations from other hospitals, and the patients were mainly treated elsewhere. After excluding invalid cases, a total of 78 valid cases remained, including two cases where the diseases relapsed. These cases were analyzed separately as their own cases.

The normalization of hCG level was analyzed by dividing cases to four categories depending on the time (in months) it took for the level to normalize: $x \leq 2$, $2 < x \leq 4$, $4 < x \leq 6$, $x > 6$. Hydatidiform moles were categorized either as complete or partial moles. Cases that were separated to be neither complete nor partial in the medical records, were considered to be complete moles. When analyzing malignant, neoplastic disorders, they were divided to persistent moles, invasive moles or choriocarcinomas. A persistent mole was considered to be a hydatidiform mole that had not penetrated into the myometrium, but chemotherapy was required for its treatment, whereas an invasive mole accounted for a mole that had invaded into the myometrium.

4 RESULTS

The research data included 78 cases with two relapsed cases, making it altogether 76 patients suitable for this study. These patients were suffering from gestational trophoblastic diseases and were treated at TAYS between years 2002 and 2013. 59 (75.6%) cases were benign hydatidiform moles, 36 of these being complete and 23 partial moles. The rest of the cases, 19 (24.4%), were neoplastic: 13 persistent moles, 3 invasive moles and 3 choriocarcinomas. All the choriocarcinomas and one of the invasive moles were considered to be high-risk diseases, whereas all the persistent moles and the other two invasive moles were low-risk diseases. All neoplastic cases were post-molar, except one of the choriocarcinomas, which was a postpartum case following a full-term pregnancy. Only two of the persistent moles followed a partial mole, whereas with other neoplastic cases, the antecedent pregnancy was a complete mole. There were no placental-site tumors treated at TAYS between 2002 and 2013.

Table 4: Frequencies of the disorders in relation to their antecedent pregnancy

			Disorder				
			Benign	Choriocarcinoma	Invasive mole	Persistent mole	Total
Antecedent pregnancy	Complete mole	Count	36	2	3	11	52
	Full-term pregnancy	Count	-	1	-	-	1
	Partial mole	Count	23	-	-	2	25
Total		Count	59	3	3	13	78
		% within all the cases	75.6%	3.85%	3.85.%	16.7%	100%

The mean age among the mothers at the time of the GTD diagnosis was 29.6 years. When including only hydatidiform moles and persistent moles in the data, a total of 23.6% of the patients belong to a group with increased risk because of the age. 11.1% of these patients were 20 years old or younger, and 12.5% were 40 years old or older. Out of all cases, the youngest patient was 16 years old with a complete mole, whereas the oldest patient was 54 years old with a persistent mole.

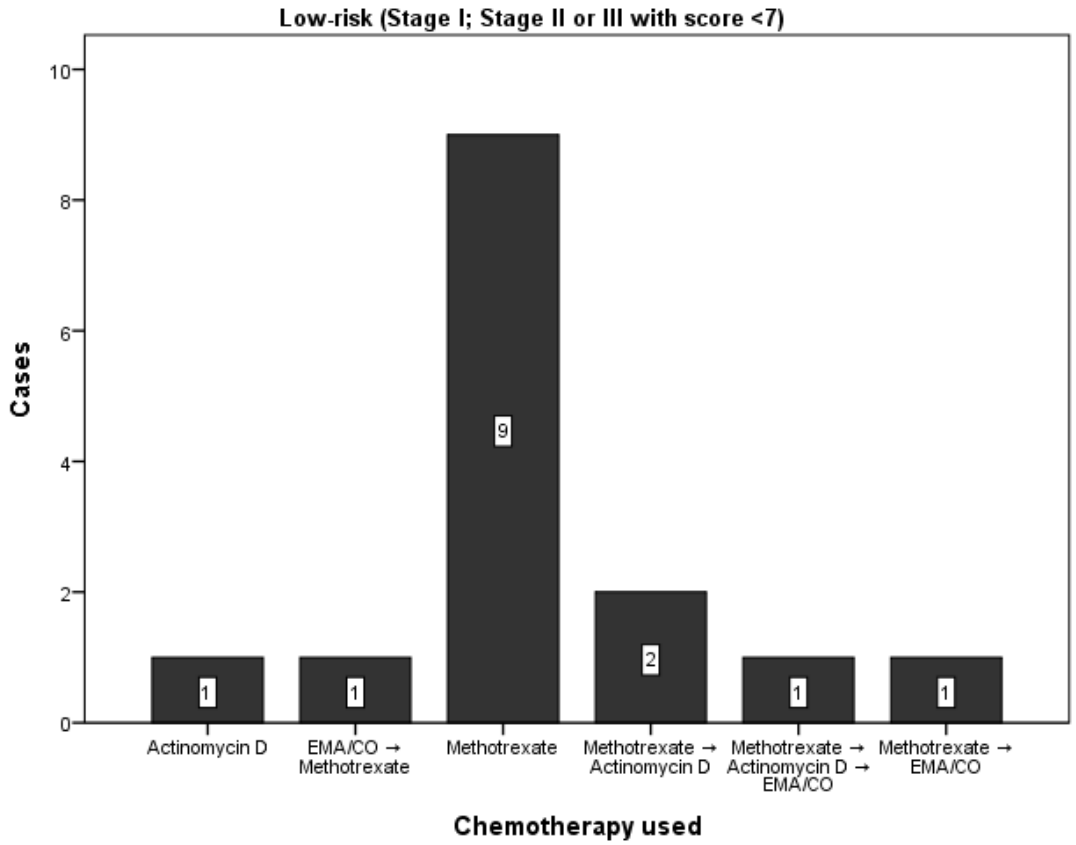
All the hydatidiform moles treated at TAYS were primarily managed with suction curettage. 91.2% of all hydatidiform moles were treated with only one suction curettage, and the rest 8.8%, needed to be evacuated twice. 47.4% of neoplastic disorders were evacuated only once, 36.8% twice, and 10.5% three times. There was also one neoplastic disorder (invasive mole) that was not evacuated at all, instead, chemotherapy was started immediately, because the case was a relapsed one. Two non-neoplastic cases had to be excluded from the analysis due to inadequate information regarding performed evacuations.

Table 5: Number of evacuations needed

			Number of evacuations needed				Total
			0	1	2	3	
Malignant/benign	Malignant	Count	1	9	7	2	19
		% within malignant cases	5.3%	47.4%	36.8%	10.5%	100.0%
	Benign (hydatidiform mole)	Count	0	52	5	0	57
		% within benign cases	0.0%	91.2%	8.8%	0.0%	100.0%
Total		Count	1	61	12	2	76
		% within all the cases	1.3%	80.3%	15.8%	2.6%	100.0%

The mean value of the hCG level before the first evacuation was 211 113 IU/l (SD: 244 498) including all the valid cases. The highest value preceding the first evacuation was over 1 000 000 IU/l. The patient in question had a partial mole, which developed into a persistent mole. The lowest value was 1 200 IU/l belonging to a patient with a partial mole treated with one evacuation. Altogether 11 cases had to be ruled out of the analysis because the information regarding their pretreatment hCG level was not available due to the initiation of the treatment in some other hospital. In addition, some of the excluded cases were initially diagnosed to be miscarriages, and therefore the hCG level was not measured before the evacuation. The average value before the evacuation number two was 10 586 IU/l, including both benign and malignant disorders that required second evacuation. The highest value was 29 211 IU/l and lowest 208 IU/l, both with partial moles. One case had to be excluded from the analysis because of inadequate information regarding hCG values. No connection between the pretreatment hCG level and the need for a second evacuation was found.

Altogether 19 neoplastic cases were treated with chemotherapy. The research data included 15 low-risk disorders and 4 high-risk disorders (Table 2). At TAYS, low-risk disorders were primarily treated with single-agent chemotherapy (either methotrexate or actinomycin D), whereas high-risk disorders were managed with multidrug chemotherapy (EMA/CO), just like described in other studies (1, 2, 3, 4, 5).

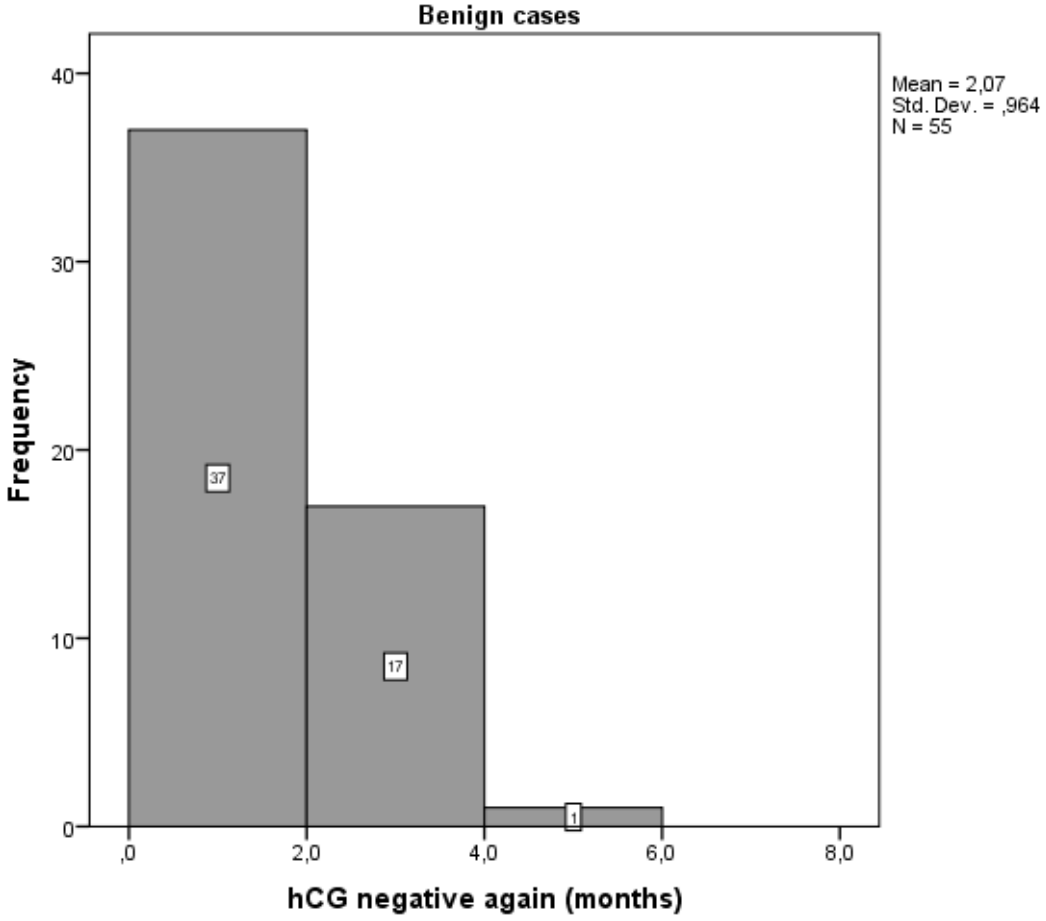


In 13 of the low-risk cases, the treatment was initiated with methotrexate. There were two methotrexate protocols used: a smaller dosage of methotrexate (0.4 mg/kg/d, maximum 25 mg/d, IM or IV) given on days 1-5, with cycles of 14 days, or higher dosage of methotrexate (1 mg/kg/d IM or IV) given on days 1, 3, 5, and 7 with folinic acid (0.1 mg/kg/d) given on days 2, 4, 6, and 8 every other week. The latter of the protocols was slightly more used: 8 patients out of 13 were treated with it. 9 out of these 13 cases were carried out with only methotrexate. In other cases, methotrexate had to be changed to another type of chemotherapy. Twice, actinomycin D was initiated because of difficult side effects of methotrexate. Once, methotrexate was changed to actinomycin D, which in turn was changed to multidrug therapy (EMA/CO), because the response for single-agent therapy was too weak. Once, EMA/CO was started after a couple of methotrexate cycles because of inadequate efficiency of methotrexate. The maximum of methotrexate cycles needed was 9 and the minimum 3–4, when it was the only drug used. One of the low-risk cases was treated only using actinomycin D for 5 days (0.5 mg/d IV), every other week for 5 cycles. Once a relapsed case, classified as a low-risk disease, was treated with EMA/CO straight from the beginning, and only the last two cycles, after normalization of the hCG level, were carried out with methotrexate because of the difficult side effects caused by the multidrug therapy.

All of the high-risk cases were initially treated with multidrug therapy EMA/CO consisting of etoposide (100 mg/m^2 IV; days 1–2), methotrexate (300 mg/m^2 IV for 12 h; day 1), actinomycin D (0.5 mg IV; days 1–2), folinic acid (15 mg x 2 PO; days 2–3), cyclophosphamide (600 mg/m^2 IV; day 8) and vincristine (1 mg/m^2

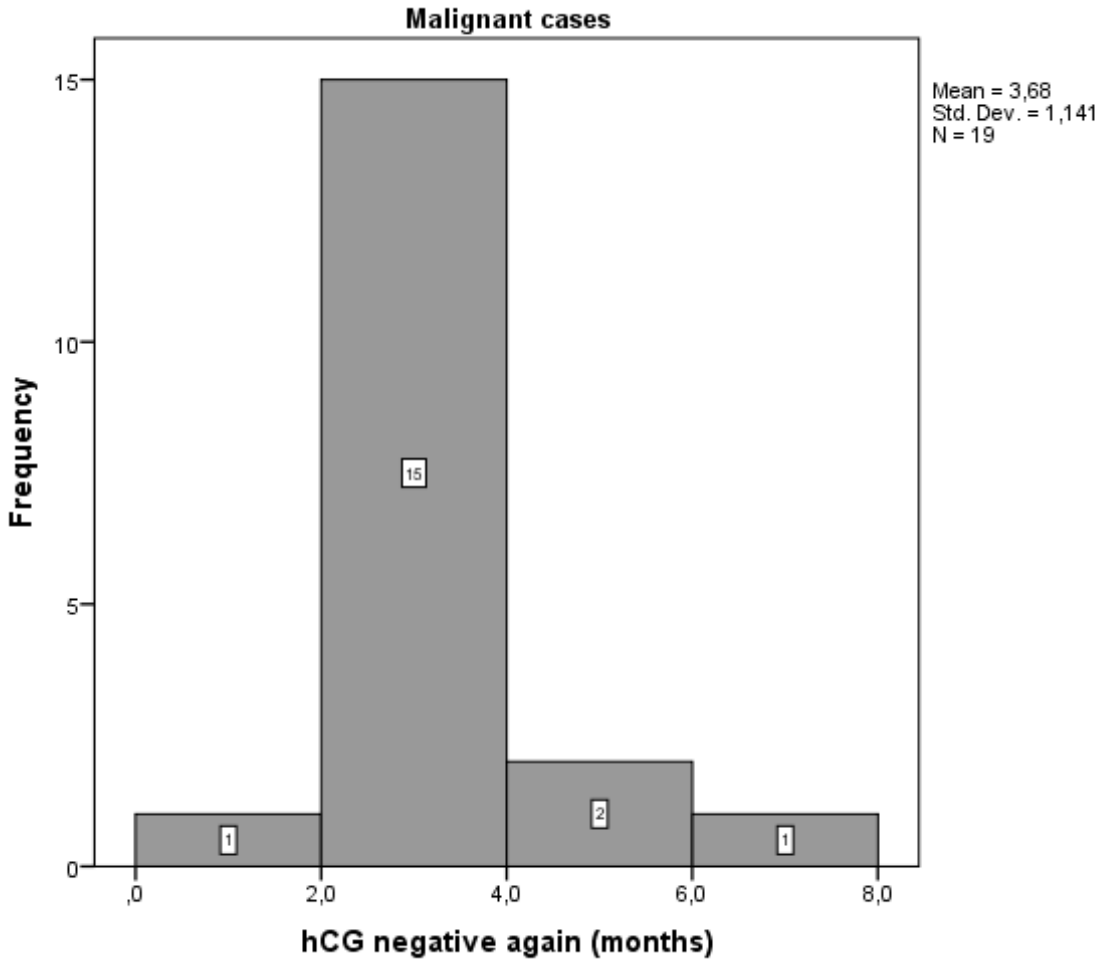
IV; day 8) given every other week. Once methotrexate had to be stopped, because it caused a transient loss of vision, and the treatment was at the end carried out as EA/CO. The rest of the high-risk cases were successfully treated with EMA/CO. When treating the high-risk diseases, the maximum of EMA/CO cycles required was 8 and the minimum 4.

The normalization of the hCG level was categorized into four different groups depending on the time (in months) it took for the concentrations to normalize (below 5 IU/l): $x \leq 2$, $2 < x \leq 4$, $4 < x \leq 6$, $x > 6$.



Histogram 1: Normalization of hCG in months (benign cases)

Histogram 1 shows that 67.3% (37) of the benign cases belong to the first group, with a normalized hCG level within the first two months after the evacuation. The rest of the benign cases belong to the second group, except for one case where it took 5 months for the hCG level to normalize. Four cases had to be ruled out from the analysis because of inadequate information regarding the hCG level normalization.



Histogram 2: Normalization of hCG in months (malignant cases)

The majority (15; 78.9%) of the malignant cases belong to the second group, where the hCG level normalized between second and fourth month after the evacuation. There was one case, a choriocarcinoma, where it took only two months for the hCG level to normalize. With one persistent mole, the normalization occurred seven months after the evacuation.

The most common side effects caused by methotrexate were stomatitis, rise of the aminotransferase level and either pain or dryness in the eyes. Two patients also described a feeling of dyspnea, and with another one of these patients, the treatment had to be carried out with actinomycin D. Multiple single side effects were reported during the use of methotrexate (Table 6). The most common side effect of actinomycin D described at TAYS, was nausea. Additionally, during the chemotherapy, one patient suffered from oral pain, alopecia, rise of aminotransferase levels, cough, urine tract infection and pneumonia. All side effects described with actinomycin treatment are presented in Table 6. At TAYS, EMA/CO was most often connected with neutropenia and paresthesia in peripheral parts of limbs. Multiple other side effects described with the use of EMA/CO are presented in Table 6.

Table 6: Side effects of the chemotherapies

Chemotherapy	Side effect	Times reported
Methotrexate (used 14 times)	stomatitis	4
	aminotransferase rise	3
	eye pain or dryness	3
	mucositis (genitals)	2
	stomach pain	2
	dyspnea	2
	fever	1
	nausea	1
	neutropenia	1
	cough	1
	urticaria	1
	brownish fluor	1
Actinomycin D (used 4 times)	nausea	2
	fatigue	1
	brownish fluor	1
	oral pain	1
	cough	1
	rash	1
	alopecia	1
	aminotransferase rise	1
	pneumonia	1
	urine tract infection	1
EMA/CO (used 7 times)	neutropenia	6
	paresthesia of peripheral limbs	3
	aminotransferase rise	2
	stomatitis	2
	pneumonia	2
	fever	2
	brownish fluor	2

	anemia	1
	constipation	1
	alopecia	1
	impairment of memory and concentration	1
	hot flashes	1
	mucositis	1
	headache	1
	lymph node pain	1
	fatigue	1
	sinusitis	1
	phlebothrombosis	1
	leukemia	1
	transient loss of vision (caused by methotrexate)	1
EA/CO	neutropenia	1
	rash	1
	glutamyltransferase rise	1

In addition to the side effects described earlier, few more severe side effects occurred at TAYS, as seen in Table 6. One of these was a transient loss of vision caused by methotrexate when a patient with choriocarcinoma was treated with EMA/CO. The loss of vision lasted for couple of hours, and the use of methotrexate was stopped immediately. The treatment was carried out as EA/CO, without methotrexate, until the patient recovered from choriocarcinoma, and no long-term harm was caused to the patient. Another patient, with choriocarcinoma as well, suffered from a secondary malignancy, an acute lymphatic leukemia, following the EMA/CO treatment. The leukemia was diagnosed a few months after EMA/CO was used, and with chemotherapy and allogenic stem cell transfusion, a remission was accomplished. Simultaneously with leukemia diagnosis, the patient was also diagnosed with phlebothrombosis. Despite the gravity of these side effects, the patient fully recovered and had a successful pregnancy with donor ovum some years after choriocarcinoma and leukemia.

After excluding five cases with insufficient information regarding pregnancies after gestational trophoblastic disease, a total of 74% of the patients have had one or more successful pregnancies, or were pregnant when the data was collected (autumn 2014). Hysterectomy was performed to two patients in accordance to their own wish. One of these patients suffered from a persistent mole and another from a partial mole. When it comes to the rest of the cases, it is impossible to say whether there has been a connection between GTD and its treatment and the lack of following pregnancies, due to inadequate information.

A relapse occurred in three of the cases. However, one of the relapses was not treated at TAYS. All patients with relapsed disease fully recovered with appropriate treatment, including the case that was treated elsewhere. Altogether, all the patients in the research data cured, and no deaths occurred. Furthermore, no long-term harm followed either from gestational trophoblastic diseases or their treatment.

5 DISCUSSION

A previous study, carried out in Finland between years 1962 and 1983 (published 1986), suggests that malignant trophoblastic diseases can be successfully treated in small units of gynecologic oncology if the knowledge of the modern cytotoxic principles is up to date.(10) The gynecologic unit at TAYS is a medium size unit. Very similar results can be received when comparing these two studies, meaning that the treatment in a medium size unit, such as TAYS can be very successful with appropriate, up-to-date knowledge as also suggested by the previous study considering smaller centers (10).

Other studies suggest that a risk for hydatidiform mole is greater when it comes to extremities of maternal age, meaning ages under 20 or over 40 years old (2, 8, 9). In this study, altogether 23.6% of the patients had a higher risk for hydatidiform mole due to their age. An advanced maternal age is also considered to be a risk factor for choriocarcinoma (8). This study included only three cases of choriocarcinomas and no connection between advanced maternal age and incidence of choriocarcinoma was found.

The majority of benign (91.2%) cases and 47.4% of malignant disorders were evacuated only once. There was also a large number of malignant disorders evacuated twice (36.8%), while benign cases managed with two suction curettages are notably fewer (8.8%). In addition, no benign cases needed to be evacuated three times. Based on these results, a conclusion can be made that neoplastic disorders treated at TAYS required more evacuations than benign, non-neoplastic disorders.

Some studies suggest that more than a half of patients with a hydatidiform mole have a completely normal hCG level within 2 months of the evacuation (2, 8). As seen in Histogram 1, the same results were achieved at TAYS, with 67.3% of benign disorders having concentrations below 5 IU/l within 2 months. With the majority of the malignant cases (78.9%), the hCG level normalized between the second and fourth month after the evacuation (Histogram 2). In addition, there was one malignant case where normalization occurred in two months and one case where it took seven months for the hCG level to normalize. Based on these results, a conclusion can be made that the normalization of the hCG level is faster in hydatidiform moles (benign, non-neoplastic) than with malignant disorders treated at TAYS.

The most common side effects of methotrexate described in other studies are stomatitis (1), mucositis, myelosuppression, rise of aminotransferase levels and pleural pain (2). All of these same side effects, except for pleural pain, were also common in TAYS when patients were treated with methotrexate. In addition, dryness or pain in the eyes was quite commonly described. With actinomycin D, the most commonly described side effect was nausea. Other single side effects were also reported. In other studies, the most common side effects of actinomycin D are nausea, alopecia (1, 3, 4) and vomiting (4). Other studies suggest

that the most common side effects of EMA/CO are nausea, hair loss and myelosuppression (2). At TAYS, multiple different side effects were reported with EMA/CO. Especially neutropenia and paresthesia of peripheral parts of the limbs were commonly reported, whereas alopecia was reported only once with the use of EMA/CO, and nausea was not reported at all. (Table 6)

To minimize the potential bias in the study, the sample size was as large as possible by including all the cases treated at TAYS between 2002 and 2013. In addition, all the cases with inadequate or unclear information were excluded from the analysis or parts of it. A small bias can be caused by possible mistakes made during the registering of the medical records, or collection of the data. Because of the severity of the disease, all patients except one remained in care for the entire follow-up.

6 CONCLUSIONS

All the patients suffering from gestational trophoblastic diseases treated at TAYS between years 2002 and 2013 were cured completely, and no long-term harm was caused by the disorders or the treatments. In addition, 74% of the patients have had a successful pregnancy following the gestational trophoblastic disorder, including those who were pregnant at the time the data was collected (autumn 2014). Based on these results, a conclusion can be made that the cure rates accomplished with treatment at Tampere University Hospital, considering both benign and malignant gestational trophoblastic diseases, are comparable to cure rates suggested in other studies (1, 2, 5, 6, 7).

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