Gestational trophoblastic neoplasia with concurrent metastasis to the mother and child: a systematic literature review

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Abstract

Gestational trophoblastic neoplasia (GTN) arising in the placenta and presenting as a metastatic disease concurrently in the mother and the baby is extremely rare. GTN poses a diagnostic dilemma to the treating clinicians. In the current review, an electronic search of Scopus, PubMed, Embase and other databases was conducted for case reports and case series of GTN co-existing or metastatic to both the mother and the baby, published to date. Globally, a total of twenty-two cases of GTN with metastasis to both the mother and baby was found. The previous history of histopathology confirmed molar pregnancy was present in 4/22 cases. The median time to diagnose GTN in the mother was six weeks post-partum. In the majority of cases, diagnosis of maternal disease was made after the infant presented with clinical manifestation. Overall survival was reported in 17/22 mothers up to varying latest follow-up and in 6/22 infants. A knowledge of the varied clinical presentation, eliciting a history of previous pregnancy loss/term pregnancy and serum beta human chorionic gonadotrophin (β-hCG) estimations were helpful for early diagnosis. The concurrent presence of GTN in the mother and baby is a rare entity and poses a diagnostic dilemma. Diagnosis in the mother often follows diagnosis in the baby after an infant presents with clinical manifestations. GTN is a highly chemo-sensitive tumour, but the main prognostic factors determining survival are the time to diagnosis following previous pregnancy and serum β-hCG levels.

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Introduction

Gestational choriocarcinoma is a malignant trophoblastic tumour arising from any gestational event. It is generally observed in reproductive-age females. Choriocarcinoma (CC) is often a clinical masquerade, and almost every case has a distinct clinical presentation in different individuals, making diagnosis difficult. Gestational trophoblastic neoplasia (GTN) may present after any gestational event, be it normal delivery, miscarriage or, rarely, a partial mole coexistent with normal fetus (1). Regression of the primary tumour after metastasis is also known. However, one-third of patients may manifest complications of metastatic disease. CC is a highly chemo-sensitive tumour, responding well to chemotherapy with a response rate of up to 80%, even in the presence of brain metastasis (2). The predominant determinant of survival is the time to diagnosis from the presentation (3).

Primary infantile or neonatal CC is an extremely rare condition, and most of the cases presenting in infancy are metastatic CC from the placenta to the fetus (4). Infantile CC usually presents between 0 and six months of age with the clinical picture of anaemia and hepatomegaly (5), which was characteristically described in 1968 by Witzleben and Bruninga (6). Commonly, the manifestations are widespread and rapidly progressing metastatic disease involving the lungs, brain, and subcutaneous tissue. Sometimes, precocious puberty may be present, related to the elevated serum beta human chorionic gonadotrophin

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(β-hCG). The unusual tendency of infantile malignancies to seed cutaneous tissue can generate vivid clinical presentations (5). The prognosis of infantile CC is usually unfavourable, with most cases being fatal within three to four weeks of diagnosis (7).

GTN arising in the placenta and presenting as a metastatic disease concurrently in the mother and the baby is extremely rare. It is observed that approximately 5% of all cases of intra-placental CC have metastasis in the fetus (7). Most mothers of babies with infantile CC are asymptomatic during pregnancy, the diagnosis being confirmed retrospectively with manifestations in the infant (7). Due to the condition's rarity, the literature available is only in the form of case reports. We report a systematic review of the literature search that yielded 22 case reports of concurrent CC in mothers and infants. The primary aim was to identify clinical signs and symptoms that can facilitate the early clinical suspicion of CC, and prompt timely investigation and appropriate therapy, thereby improving survival in both the mother and baby.

Material and Methods

Being a systematic review of case reports, ethics committee approval was not sought as systematic reviews are exempt from ethics review. The systematic review was planned and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.

An electronic search of Scopus, PubMed, Embase and other databases was conducted for case reports and case series of GTN co-existing or metastatic to both the mother and the baby, published to date. The electronic search strategy was done using keywords such as "gestational trophoblastic neoplasia" OR "choriocarcinoma" OR "infantile choriocarcinoma" OR "placental site trophoblastic tumour" OR "PSTT" and "mother and baby" OR "mother and fetus" and "case reports" OR "case series" OR "concurrent choriocarcinoma" OR "infantile metastatic choriocarcinoma". We analyzed the title and abstracts of all case reports identified by the initial search. The reference lists of relevant reports were also explored. Two reviewers double-checked the data independently and simultaneously to avoid duplication. The third reviewer resolved any conflicts.

Published case reports and case series of GTN co-existing or metastatic to both the mother and the baby, published from inception till September 2022, were included in this systematic review. GTN cases localized to the placenta or confined only to the mother or the fetus were excluded. Patients of all published case reports/case series of infantile CC only were studied in detail for the information regarding the mother so that no cases of the concurrent disease in mother and infant were missed. Review articles, original articles, clinical trials, conference abstracts, editorials, cases with incomplete information, and papers in languages other than English or commentary were excluded.

We extracted information, such as geographical distribution or country of occurrence of the case, year of publication, and the type of GTN. Details of the mother, including her obstetric history, with particular attention to the previous history of molar pregnancy or CC, were recorded. A note was made of what brought the patient to clinical attention, their clinical features, serum β-hCG levels at the time of diagnosis, sites of metastasis and their follow-up, survival and treatment received. Information regarding the baby included the sex, age of presentation, presenting complaints, how and when the diagnosis was confirmed, serum β-hCG levels at the time of diagnosis, sites of metastasis and the outcome. A note was also made of the primary misdiagnosis, if available.

Descriptive statistics were used to calculate simple frequency, percentage, and proportion out of the total case reports. The survival analysis was performed by Kaplan Meier analysis, using the Statistical Package for Social Sciences for Windows, version 16 (IBM Inc., Armonk, NY, USA). Death was taken as the event for overall survival (OS) analysis.

Results

A total of twenty-two cases of GTN with metastasis to both the mother and baby had been reported globally (Figure 1). Of these, 21 cases were of CC, and one was a placental site

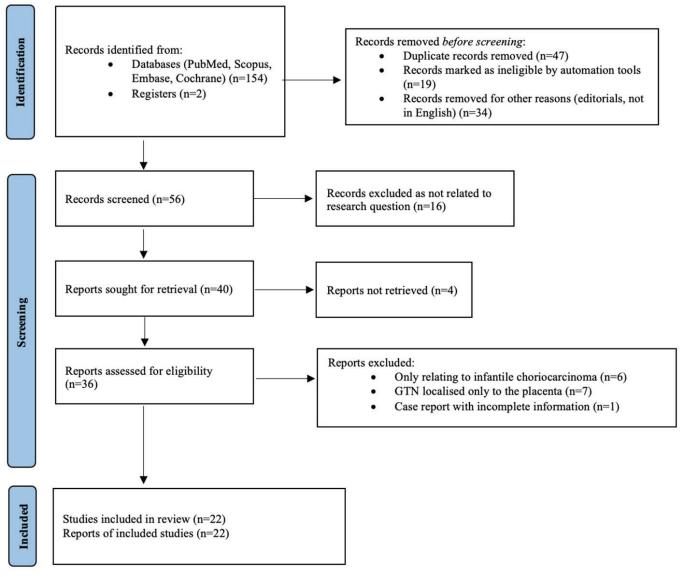

Figure 1. PRISMA flowchart of the screening process used for the present systematic review
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses

trophoblastic tumour (PSTT). Out of these 22 children reported, the male:female ratio was 1.2:1. The median birthweight was recorded in 14 children whose data was available as 2965 grams [interquartile range (IQR): 2615.5, 3325]. The case details are shown in Table 1, 2, respectively.

Previous molar pregnancy

The previous history of histopathologically confirmed molar pregnancy was present in 4/22 cases. Furthermore, in 3/22 cases, a history of prior molar pregnancy cannot be excluded as the author has reported that the patient had a history of abortion before the index pregnancy. Nevertheless, no details regarding the histopathology report of the products of conception were reported. There was no history of previous molar pregnancy given in 9/22 cases. In 6/22 cases, the details regarding the last pregnancy were not mentioned.

Time of diagnosis in mother and baby

The median time to diagnose GTN in the mother was six weeks post-partum. Two out of these twenty-two cases were diagnosed at the time of delivery, both due to the abnormal gross appearance of the placenta, for which a pathological examination was requested. In one case, the diagnosis was suspected in the antenatal period at around 36 weeks of gestation due to multiple lung metastases. In one case, the diagnosis was made at thirteen months after delivery on β-hCG follow-up; the patient, in this case, was on follow-up because of a diagnosis of infantile CC in the baby. The median age of presentation in infants was 1.75 (IQR: 0.1, 6.75) weeks. The median age of diagnosis in the child was 5.00 (IQR: 3.55, 8) weeks. In 10/22 children, the diagnosis was suspected at birth. For 1/22 children, the diagnosis was suspected because the mother was diagnosed with GTN. In the remaining 21 children, the primary diagnosis was made in the infant, and retrospectively mother was diagnosed as having the disease. The median time to diagnosis from symptom onset was 1.7 (IQR: 0, 3.65) weeks in the infants.

What brought the patient to clinical attention?

In 8/22 cases, the diagnosis was suspected after the infant presented with symptoms. In 4/22, dilatation and curettage due to abnormal uterine bleeding led to pathologic confirmation in the post-partum period. In 6/22, the diagnosis was suspected either after imaging or β-hCG estimation was done for a tumour of unknown origin, which showed widespread metastasis. In five cases, the diagnosis was suspected in the peripartum period, predominantly due to abnormal gross appearance of the placenta or post-partum haemorrhage after delivery (2/22) and significant feto-maternal haemorrhage (1/22). In one case, the patient was on β-hCG follow-up due to a previous history of molar pregnancy.

In infants, the primary complaints at the time of presentation were pallor, vomiting, skin nodules, and poor feeding observed in 11/22 (50%), 3/22 (13.7%), 2/22 (9%), and 2/22 (9%), respectively. Intrauterine foetal demise was noted in 2/22 (9%). Hematemesis, melena, abdominal distension, generalized swelling and cold were each observed in one child. Hepatomegaly was observed in 13/22 (59%). Other clinical findings were failure to thrive, facial mass, jejunal mass and cutaneous tumours, each in one child. Complications noted were severe anaemia (haemoglobin <8 g/L) in 11/22 (50%), respiratory failure, tumor bleeding and cardiac failure in 3/22 (13.7%) each, and respiratory distress, intracranial haemorrhage, and multi-organ dysfunction in 2/22 (9%) each. Complications, such as pneumothorax, hypovolemic shock, hemoperitoneum, severe acidosis, thrombocytopenia, tumor rupture, pulmonary haemorrhage and hypoproteinaemia were each recorded in one child. The liver was involved in 17/22 (77.35%). Metastases to the lung were recorded in 16 (72.7%), brain and gastrointestinal tract in 4 (18.2%), bone and skin/subcutaneous site in 3 (13.7%), eyes in 2 (9%) and kidney in one child.

The diagnosis of CC was made post-mortem in 9/22 (40.9%) infants by autopsy or post-mortem histopathology of liver mass. The antemortem diagnosis was made in 13 children; seven by biopsy of the mass, four by β-hCG estimation and two by a combination of biopsy and β-hCG. The possibility of CC was strongly considered in 4 children (18%). Before arriving at the final diagnosis, the differential diagnosis was available for 20 children and included hepatic angiosarcoma, haemangioma, hepatoblastoma, haemolytic anaemia, feto-maternal haemorrhage, haemangioblastoma, haemangioendothelioma, hepatocellular carcinoma, and sepsis in 3, 3, 2, 2, 2, and 1 child, respectively.

Treatment received

The details of treatment were available for 20 mothers. Chemotherapy alone was provided in 13, chemotherapy and surgery in four, chemotherapy and irradiation in one, and surgery alone in two. In three patients, single-agent methotrexate (MTX) was administered, while the rest received combination chemotherapy. In four patients, MTX, actinomycin and etoposide combination chemotherapy was provided. Other drugs used were cisplatin, cyclophosphamide, and vincristine.

Definitive treatment was administered in 14 children (63.7%), which included chemotherapy alone in seven, a combination of chemotherapy and surgery in five and surgery only in two children, respectively. The most common treatment regimen

Table 1. Gestational trophoblastic neoplasia co-existing in mother and baby: Maternal characteristics

S. no	Author, year of publication	Previous h/o molar pregnancy	When the diagnosis was made? (weeks post-partum)	How was diagnosis made?	Symptoms in the mother at diagnosis	Maternal serum β-hCG at diagnosis	F/u of mother	Treatment received
1	Mercer et al. (8), 1958	Not mentioned	8 weeks	Dilatation and curettage due to AUB	Bleeding p/v off and on since 6 wk. pp	NA	Death at 8 months pp	TAH + BSO followed by immediate cobalt teletherapy and full course of pelvic irradiation
2	Brooks and Nolting (2), 2014	Not mentioned	6 weeks	After confirmation of diagnosis in the baby	Not mentioned	Not mentioned	Not specified	CT (details not available)
3	Hanson et al. (9), 2011	Not mentioned	6 weeks	After confirmation of diagnosis in the baby	Not mentioned	>60,000 mIU/mL	Survived	Total abdominal hysterectomy f/b chemotherapy (Single agent MTX X 8 doses)
4	Sashi et al. (10), 1996	Yes	7 weeks	After death of baby, multiple lung and liver tumours and raised high urine hCG	Not mentioned	Urine hCG - 435.84x 104 IU/L)	Survived till14 months from diagnosis	CT (details not available)
5	Andreitchouk et al. (11), 1996	Yes	4 months	Clinical features. After death of baby, its autopsy report	General fatigue, back pain, and intermittent genital bleeding, severe weight loss and abdominal distention, Hepatomegaly, Severe anaemia	Urine hCG, 5,300,000 mIU/mL; Serum hCG, 4,358,400 mIU/mL Serum hCG-P, 20,000 ng/mL	Remission	Chemotherapy (EMACO X 14 courses in 7 months (Etoposide, 100 nig/m^2/day on days 1 and 2; Methotrexate, 100 mg/m^2/day on day 1; Dactinomycin, 0.5 mg/m^2/day on days 1 and 2 Cyclophosphamide, 600 mg/m^2/day on day 9 Vincristine 1 mg/m^2/day on day 9 and combined with folic acid 30 mg/day on days 2, 3, 4
6	Avril et al. (12), 1986	No	At delivery	Pathologic examination of placenta due to a 5 cm abnormal growth on the uterine surface.	NK	16,000 IU/L	Alive at 14 months No further details available	Chemotherapy with methotrexate, actinomycin D, vincristine, and cisplatinum.

Table 1. Continued

7	Bolze et al. (13), 2013	No	13 months	On β-hCG follow-up after diagnosis in baby	Intermittent headache, partial loss of vision, elevated β-hCG	107 IU/L	Normal at 3 years f/u. No evidence of relapse on MRI, PET and hCG levels at 3 years follow-up	Resection of brain metastasis + chemotherapy with etoposide, actinomycin D and cisplatinum (3 courses) + stereotactic brain irradiation (39 grays in 13 fractions)
8	Flam et al. (14), 1989	No	10 weeks	D and C d/t persistent bleeding	PPH at 4 weeks pp	24,200 IU/L	Alive at 7 years	Chemotherapy (methotrexate and folinic acid) 3 cycles. hCG not detectable after second cycle
9	Rzanny-Owczarzak et al. (15), 2021	H/o abortion 4 months before present pregnancy, HPE NA	5 weeks	After diagnosis in baby, D and C done in mother	Vaginal bleeding	37,600 IU/mL	Alive and pregnant at 1 year	Chemotherapy for 6 months (dactinomycin, etoposide, methotrexate)
10	Liu and Guo (16), 2006	H/o three abortions before current pregnancy	5 weeks	D and C i/v/o persistent vaginal bleeding	At the 24th, 29th and 37th day postpartum, the patient had unexplained vaginal bleeding	hCG-33648 mIU/mL at day 51, and the β-hCG-14899.9 mIU/mL	Normal at 1 year f/u	Uterine arteriography and transcatheter arterial chemotherapy (VCR + FUDR + KSM + VP16)
11	Tsukamoto et al. (17), 1986	H/o 2 abortions, No h/o molar pregnancy	3 weeks	β-hCG done after confirmation of fetal diagnosis on autopsy.	Intermittent bloody discharge p/v	1270 rig/mL at 4 weeks, 1590 rig/mL at 5 weeks, Urinary hCG 3000 IU/L at 3 weeks, 5000 IU/L at 4 weeks	Asymptomatic at 9 months f/u	Combination chemotherapy with MAC 7 courses (methotrexate 15 mg im, actinomycin-D 0.5 mg iv, and cyclophosphamide 100 mg iv q.d. x 5 days), X 7 weeks 50 mg of methotrexate was injected into each internal iliac artery.
12	Buckell and Owen (18), 1954	No	9 weeks	Had Abnormal uterine bleeding post-delivery, D and E done for retained products of conception, HPE suggestive	Continuous vaginal bleeding for 9 weeks following birth		Alive at 13 months pp	TAH, BSO and pelvic RT

Table 1. Continued

13	Kruseman et al. (19), 1977	No	4 weeks	FMH Autopsy of fetus s/o CC Secondary PPH at 4 weeks d/b D and C	PPH at 4 weeks pp	345,000 IU/24-hour urine	Alive at 6 months	9 courses of CT (methotrexate and folinic acid)
14	Mosayebi and Movahedian (20), 2016	No	6 weeks (after death on autopsy)	Severe anaemia and fatigue in pregnancy	Not mentioned	Not mentioned	Died at 30 days pp	None
15	McNally et al. (21), 2002 Heath and Tiedemann (22), 2001	Yes	At delivery	H/o molar pregnancy, Abnormal appearance of placenta	Not significant	12,34,000	Alive and healthy at 3 years	Craniotomy + EMA/EP regime (etoposide, methotrexate and actinomycin D alternating weekly with cisplatin and etoposide) 6 cylces + 2 cycles of intrathecal methotrexate f/b 7 cyles of etoposide and paclitaxel f/b 3 cycles of paclitaxel
16	Daamen et al. (23), 1961	No	5 months	Primary and Secondary PPH at delivery f/b palpable tumour at 5 months pp.	A large round, taut and cystic tumour filled the entire true pelvis and was continuous with the neoplasm palpable from the outside, Arising from right ovary		Died 7 months pp	Laparotomy f/b chemotherapy with methotrexate
17	Aozasa et al. (24), 1981	Details not available		Chest X-ray s/o multiple metastasis and elevated β-hCG	A varix was noted on uterus at the time of delivery, Pyrexia, amenorrhea, Sudden unconsciousness and death	1280 IU/L	Died at 5 months pp	Not mentioned
18	Fraser et al. (25), 1992	Not mentioned	5 weeks	Elevation in β-hCG		8 weeks pp-day 0-2000, day 11-950, day 20-300, and day-37-1450	Alive and healthy at 2 years	4 courses of cisplatinum and VP 16

Table 1. Continued

19	Getrajdman et al. (26), 2012	No	1 month postpartum During pregnancy at 36 weeks was suspected	CT scan s/o metastasis in lung, liver and spleen a/w elevated β-hCG	Cramping at 12 weeks, Haemoptysis at 28 weeks, and rib pain at 36 weeks. Later again presented 1 month pp with debilitating shoulder pain, shortness of breath and abdominal distension	4.9 million mIU/mL	Alive and healthy at 2 years	Emergent selective hepatic embolization and splenic artery embolization f/b CT with EMA-EP alternatively for 6 weeks
20	Kishkurno et al. (27), 1997	Yes	13 weeks	Large liver and lung tumours with elevated hCG	Large hepatic tumour and small multiple metastases to the lungs	Urinary 4,213,500 IU/L	Alive and healthy	CT
21	Picton et al. (28), 1995	Not mentioned	8 weeks	Heavy vaginal bleeding, multiple lung metastasis with elevated hCG	Heavy vaginal bleeding with clots for 8 weeks	1112000 IU/L	Alive and healthy at 11 months	CT with methotrexate with folinic acid rescue followed by IV actinomycin-D and etoposide for 3 days for 6 cycles
22	Monclair et al. (29), 2002	h/o 2 abortions, HPE not mentioned	8 months	D and C following recurrent vaginal bleeding	Irregular vaginal bleeding	1270 IU/L	Alive and healthy at 26 months	TAH

GTN: Gestational trophoblastic neoplasia, CC: Choriocarcinoma, PSTT: Placental site trophoblastic tumour, CT: Chemotherapy, RT: Radiotherapy, hCG: Human chorionic gonadotropin, NK: Not known, NA: Not available, D and C: Dilatation and curettage, HPE: Histopathologic examination, FMH: Feto-maternal haemorrhage, PPH: Postpartum haemorrhage, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, pp: Postpartum, MAC: Methotrexate, actinomycin-D and cyclophosphamide

used was bleomycin, etoposide, and cisplatin in four children. MTX alone and dexamethasone doxorubicin combination were used in two children, respectively. A combination of MTX, etoposide and cisplatin, etoposide and MTX, etoposide alone and a combination of multiple drugs were administered in one child each. Complications secondary to chemotherapy were reported in one child, which were hearing loss and adrenal insufficiency.

Follow-up and survival

The duration of follow-up mentioned in each of the cases varied widely. Excluding the 4/22 mothers who died, the follow-up time mentioned in the cases was as follows. The duration of follow-up was around one year (11-14 months) in 5/22, around two years (24-26 months) in 3/22, three years in 2/22 and seven years in 1/22. In 2/22 cases, the follow-up was less than nine months. In 4/22 cases, although the authors mentioned that the patients survived, the duration of follow-up was not mentioned. 4/22 mothers expired within six to seven months of pregnancy, with a mortality rate of 18.2%. One patient expired 30 days after delivery, one each after five months, six months and seven months, respectively. 17/22 mothers survived up to the most recent follow-up reported (shortest reported follow-up reporting survival & longest reported follow-up), and in 1/22 cases, no information regarding survival was mentioned. The 12-month OS in mothers was 71.8±10.7% (Figure 2).

Out of 20 live-born children, six (30%) survived to latest reported follow-up, ranging from seven months to three years in children who survived. The OS was 22.2±9.8% (Figure 3). Out of seven children who received multi-agent chemotherapy, including a platinum agent, six children survived (85.7%).

Table 2. Gestational trophoblastic neoplasia co-existing in mother and baby: infant details (n=22)

S. no	Author and year of publication	Presenting complaints & clinical features at time of diagnosis	Time of diagnosis in weeks	Complications	Method of confirmation of diagnosis	Site of metastasis	Treatment received	Outcome & follow -up
1	Mercer et al. (8), 1958	Small red nodule in the upper anterior alveolar ridge	6	Profuse haemorrhage	Biopsy	Upper maxilla, nasal fossa and later head and neck	Surgery	Died
2	Brooks and Nolting (2), 2014	Right-sided facial mass, Recurrence of facial mass after resection	5	Tumour bleed	Biopsy	Lung	Surgery, embolization and chemotherapy	Survived
3	Hanson et al. (9), 2011	Fever, pallor, and fatigue, Recurrent severe anaemia, hepatomegaly	8	Severe anaemia, hypovolemic shock, respiratory failure	Biopsy and β-HCG	Liver	Chemotherapy and liver transplantation	Survived
4	Sashi et al. (10), 1996	Anaemia, abdominal distension, tachycardia, cyanosis, liver tumours	5	Multi-organ dysfunction syndrome	Biopsy	Liver, lung, brain	Nil	Died
5	Andreitchouk et al. (11), 1996	Severe anaemia Hepatomegaly	5	Congestive cardiac failure, respiratory distress	Autopsy of liver mass, β-HCG	Liver, lung, brain.	Chemotherapy	Died
6	Avril et al. (12), 1986	Cutaneous lesions Disseminated cutaneous tumours, hepatomegaly, lung rales	0.85	Hypoproteinaemia, pulmonary haemorrhage	Biopsy	Skin, lung, bone, pelvis	Chemotherapy	Died
7	Bolze et al. (13), 2013	Dyspnea and anaemia, Liver mass, mediastinal lymphadenopathy	21.8	Not mentioned	β-HCG	Liver, lung, mediastinal lymph nodes	Chemotherapy and hepatectomy	Died
8	Flam et al. (14), 1989	Anaemia Liver tumour	3	Rupture of liver tumour	Post-mortem histopathology of liver mass	Liver	None	Died
9	Rzanny-Owczarzak et al. (15), 2021	Hematemesis Liver tumour	4	Multi-organ dysfunction syndrome respiratory failure	Autopsy	Lung, liver, intestine, lymph nodes	Chemotherapy	Died
10	Liu and Guo (16), 2006	Unexplained melena, Jejunal mass	3.4	Nil	Biopsy of jejunal mass	lung, jejunum,	Chemotherapy	Survived
11	Tsukamoto et al. (17), 1986	Unexplained intrauterine fetal death Metastatic liver disease	0.1	Intrauterine fetal death	Autopsy	Liver, lungs, hilar lymph nodes, diaphragm, and subcutaneous tissue of the head.	None	Intrauterine fetal death
12	Buckell and Owen (18), 1954	Vomiting, abdominal distension, Anaemia, epigastric mass	7	Severe anaemia	Autopsy	Liver, ribs and nodes	Blood transfusion	Died

Table 2. Continued

13	Kruseman et al. (19), 1977	Still birth, polyhydramnios, tumour in left kidney 1.2x1.8 cm	0.1	Massive feto-maternal haemorrhage	Autopsy	Kidney	None	Intrauterine fetal death
14	Mosayebi and Movahedian (20), 2016	Recurrent vomiting and poor feeding, sick child, decreased neonatal reflexes, systolic murmur, bilateral megalocornea and leukocoria	8	Severe anaemia, encephalopathy, intracranial haemorrhage and herniation	β-HCG and mother's diagnosis	Brain, lung, liver and eye	Blood transfusion	Died
15	Heath and Tiedemann (22), 2001	Solitary liver nodule	0.1	None	β-HCG	Liver	Chemotherapy, surgery	Survived
16	Daamen et al. (23), 1961	Fevere, severe anaemia, firm tumour in the upper abdomen, leucocytosis, recurrent anaemia, jaundice	26.2	Severe anaemia	Biopsy of liver tumour	Liver, peritoneum, abdominal muscles and skin, lung, subcutaneous layers and adrenal	Laparotomy, Chemotherapy, multiple transfusions	Died
17	Aozasa et al. (24), 1981	Weakness of feeding and edema in the right inguinal and labial region, hepatomegaly, abdominal distension, thrombocytopenia	8	Congestive cardiac failure	Biopsy of liver tumour	Liver, lung	Right hepatic artery embolization and excision	Died
18	Fraser et al. (25), 1992	Anaemia and lethargy, Hepatomegaly	9 weeks	Nil	Biopsy of liver mass, β-HCG	Liver, lung	Chemotherapy, segmental resection of liver mass	Survived
19	Getrajdman et al. (26), 2012	Pallor Hepatomegaly and anaemia	4 weeks	Tumour bleed	Elevated serum β-HCG	Liver, lung, eyes	Chemotherapy	Survived
20	Kishkurno et al. (27), 1997	Anaemia, hepatomegaly	5.4	Recurrent severe anaemia, congestive cardiac failure	Autopsy, biopsy of liver mass	Liver, brain, lung	Chemotherapy	Died
21	Picton et al. (28), 1995	Feeding difficulty, poor weight gain, anaemia, vomiting Failure to thrive, hepatosplenomegaly	4.5	Intracranial haemorrhage, respiratory failure, severe anaemia, hemoperitoneum, severe acidosis	Autopsy	Liver, lung	None	Died
22	Monclair et al. (29), 2002	General malaise, common cold, Hepatomegaly, dyspnoea, tachycardia, pneumothorax,	19.4	Respiratory failure secondary to bilateral pneumothorax	Autopsy	Liver, lung, mesentery	None	Died

HCG: Human chorionic gonadotropin, NK: Not known, NA: Not available

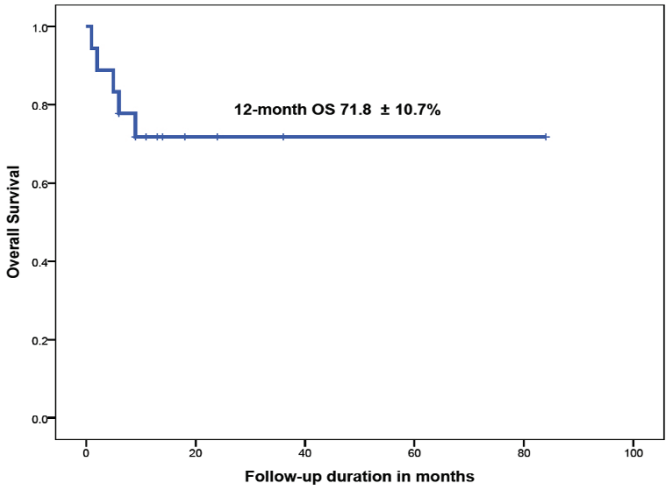

Figure 2. Overall survival of mothers with choriocarcinoma, coexisting or metastatic to the child
OS: Overall survival

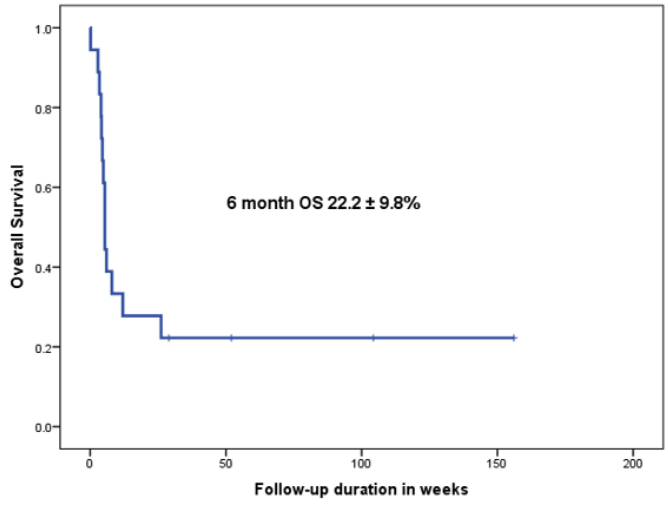

Figure 3. Overall survival of children with choriocarcinoma coexisting in the mother
OS: Overall survival

Discussion

We present a comprehensive systematic review of all published case reports and short case series of GTN co-existing or metastatic to both the mother and the baby published up to September 2022. Worldwide, only 22 such cases were published in English, indicating the rarity of this entity. Therefore, this systematic review will help understand the epidemiology, clinical presentation, and OS and prognosis of mother and baby. It would also help to identify a possible clinical clue that may help treating physician to identify the condition early, thereby improving prognosis and survival.

The transmission of maternal cancer to the fetus/neonate is an extremely rare phenomenon, with the reported incidence being one infant per 500,000 mothers with cancer (30). Approximately 1 in 1000 live births involves a mother with cancer (31). Eighteen cases have been reported in the literature (32), and the malignancies include those of the skin, lung, cervix, and hematologic system, predominantly leukaemia. Most of these reported cases are non-GTN. Either of the following hypothesis can explain the transmission of cancer from mother to the fetus/neonate. One mechanism is by transplacental hematogenous dissemination and the other by direct transmission (via contact or aspiration) at the time of delivery (33).

Though extremely rare, GTN arising from the trophoblastic tissue and metastatic to both the mother and baby can be explained by the fact that malignant tissue arising from the trophoblast can enter the systemic circulation and then through the placenta to the fetus. Trophoblastic tissue embolizing into the systemic circulation was first reported by Schmorlin in 1893 in a post-mortem study of eclamptic patients (34). There have also been isolated case reports of trophoblastic embolism during curettage or caesarean section (35,36). Trophoblastic pulmonary embolism is also common, predominantly in patients with difficult parturition, following manual removal of placenta, in cases of placenta praevia, preeclampsia and eclampsia and in cases of uterine tears (34).

GTN is considered one of those malignancies with a good prognosis because of its high chemo-sensitivity. Survival rates have been reported to vary from 85% to 95%. However, in the present review, the OS was lower as the 12-month OS in mothers was 71.8±10.7%. The six-month OS in cases where the infantile CC co-exists with the maternal CC or is a result of metastasis was 22.2±9.8%. The survival of infants was similar to that reported in previous studies, at approximately 20% (5). Still, there seems to be an earlier onset of the disease, with the median age of presentation being 1.75 weeks. In comparison Blohm et al. (5) reported age at presentation to be four weeks. Although not much studied, the disease co-existing in the mother and baby or fetal/neonatal metastasis could be an important factor determining poorer prognosis. Hence, our review found that it seems to be a more rapidly progressing disease when it co-exists in mother and baby.

We found that the median age to diagnosis in the mother was six weeks post-partum. A previous history of molar pregnancy was present in 4/22 patients. In 9/22 mothers, the last pregnancy details were either unavailable or not confirmed (h/o abortion present, but molar pregnancy not ruled out on histopathology). GTN is staged and scored as per the WHO Scoring System, which divides it into two groups: (i) low-risk group (score ≤6) intimating single-agent chemotherapy; and (ii) high-risk group (score >6) mandating multi-agent chemotherapy (37). Risk is defined as developing drug resistance (methotrexate or MTX) as determined by the WHO Prognostic Scoring System. All patients

with non-metastatic disease and patients with risk scores <7 are considered low-risk. Patients with a score >6 are deemed to have high-risk disease. It is notable that two of the parameters in the risk scoring include the antecedent pregnancy, whether it was a mole, abortion or a normal term pregnancy and the time interval from the end of index pregnancy to the diagnosis of GTN. It, therefore, becomes imperative to determine if the present GTN developed following which pregnancy, or which is the antecedent pregnancy. The tumour DNA would be identical to the neonate if it arose following the current pregnancy and will be different if the index pregnancy was a previous abortion, mole or previous full-term pregnancy. There is always a possibility that undetected gestational trophoblastic disease from an earlier pregnancy may have progressed to CC during the index pregnancy. Genetic analysis should therefore be performed to confirm the origin of the tumour, as this would confer a significant prognostic value. If the tumour is gestational in origin, it would contain both maternal and paternal genes, and its genetic composition would be the same in the mother and fetus or the neonate. This also rules out the possibility that the tumour arose de novo in the infant and is not a metastasis from the mother. The time between the index pregnancy and development of CC has been reported to range widely from 4 weeks to as long as 25 years (38). Therefore, in any adult female, the origin of GTN being a previous pregnancy always arises. At times, it may be challenging to localize the antecedent pregnancy causing GTN as the malignant placental or uterine tissue may be extruded entirely or devitalized, leaving no trace of its presence (39). Therefore, the so-called primary tumour may, in all possibility, be a metastasis. Establishing the causative pregnancy, which may also be any other than the current pregnancy, has a clear prognostic value, more so in cases of PSTT or epithelioid trophoblastic tumour, where a time interval of less or greater than four years affects future survival (40,41).

Blohm et al. (5) published one of the most extensive and informative literature reviews regarding infantile CC in 2004 (21). A few salient observations in the review included: (a) equal male-to-female ratio; (b) major clinical features of anaemia, hepatomegaly, failure to thrive, respiratory distress or pulmonary haemorrhage; (c) 33% presented in the neonatal period and 67% up to 5 months of age; (d) liver, lung, brain and skin involvement in 77%, 67%, 27% and 10%, respectively; (e) diagnosis was established at autopsy in 32% of live-born infants; (f) elevated β-hCG in all tested children that contributed to the confirmation of diagnosis; (g) anti-neoplastic therapy was administered in 15/28 live-born infants and combination chemotherapy including a platinum agent along with surgery appeared to be the most effective strategy; and (h) 5/30 children (17%) survived. In our review, the observations of equal male-to-female ratio, clinical features, sites of involvement, and proportion of live-born infants diagnosed in the autopsy were similar; however, in cases in which the infantile CC was co-existent with the maternal CC or was a result of metastasis from it, there seems to be an earlier onset of disease with the median age of presentation being 1.75 weeks. In comparison, it was four weeks reported by Blohm et al. (5). Hence, it seems to be a more rapidly progressing disease when it co-exists in mother and baby. It should be noted that 13 children reported in this review had a differential diagnosis of malignancy. The common differentials were hepatic angiosarcoma, haemangioma and hepatoblastoma. These observations highlight the lack of awareness among general paediatricians and those working in paediatric oncology regarding infantile CC, probably due to its rarity. However, severe anaemia refractory to multiple transfusions, multi-systemic involvement and multi-organ dysfunction, especially pulmonary haemorrhage in the presence of hepatic tumour, are key signs for suspecting CC in an infant, even in the absence of disease activity in the mother. In the current study, liver metastasis was the common presentation in the fetus.

The predominant localization of metastatic CC in the fetal liver can be explained easily by understanding the prenatal blood supply to the fetus. The liver gets around 70 to 80% of all the blood in the umbilical vein, and only 20-30% is shunted through the ductus venosus (42).

In CC, β-hCG is universally elevated and is a simple, easy, affordable and accessible investigation. In the reports included in this review, β-hCG was performed in only 6/20 children and was elevated in all. This observation further highlights that CC is not one of the initial differentials considered in an infant with hepatic tumours. Measurement of β-hCG can prevent a risky, life-threatening procedure like a biopsy, as CC is very friable and well-known for intrinsic tumour rupture. In seven children included in this review, doing a β-hCG measurement could have speeded and facilitated diagnosis.

Another notable finding of this review was that although all 22 reported CC in both mother and infant, in only one child, CC was suspected because of previous GTN in the mother. In most cases, the disease was suspected in the mother only after the diagnosis was made in the baby. However, on closer analysis, in 11/20 (55%) mothers in whom the time of diagnosis was available, the disease was confirmed within two weeks of diagnosis in the baby. Hence, it is plausible that the majority of disease manifestations are concurrent in mother and baby. For early diagnosis in both mother and baby, it is essential for effective communication and collaboration between healthcare providers and physicians managing mother and infant.

In adults, the management of CC is risk-stratified and tailored. Patients with low-risk disease are treated with single-agent (MTX or actinomycin D) therapy. In contrast, patients with

high-risk disease are treated with multi-agent chemotherapy and surgery or radiation as per requirement. Survival in adults is remarkable, reaching up to 100% in low-risk and 90-95% in high-risk disease (43). In our review, the superior survival of mothers, when compared to children, underlines the remarkable chemo-sensitivity of the tumour. However, CC following-term pregnancy is usually considered high-risk because of metastasis and high β-hCG levels. In a study from the Netherlands on post-term CC, the survival was 86% (44). All patients were either medium or high-risk in their cohort as per their clinical staging system. As per the country protocol, treatment was multi-agent chemotherapy consisting of EMA/CO (etoposide, MTX, actinomycin D, cyclophosphamide and vincristine). They identified a long symptom to treatment interval of 16 weeks and high MTX resistance (75%). Hence, they suggested that multi-agent chemotherapy is justified in post-term CC. Similarly, authors from China have also reported high complete remission (CR) rates of 87.8% with combination chemotherapy (45).

In children, as in other germ cell tumours, the management of CC consists of multi-agent neo-adjuvant chemotherapy, re-assessment after 2-4 cycles, surgery of persistent disease and adjuvant chemotherapy. The principle of this complex therapy is to control the metastatic nature of the disease and prevent relapse. Upfront chemotherapy helps control the disease, especially when a child has multi-systemic involvement and is not fit for surgery. The excellent survival of children treated in this fashion in this review re-iterates the principles of therapy to be undertaken. The guidelines are well-established and readily available (46).

Significant predictors of survival identified are the time to diagnosis and serum β-hCG levels (37,47). A study by Ma et al. (45) of 123 patients with post-partum CC observed an interval between pregnancy and diagnosis of fewer than four months, and a β-hCG titre less than 1000 IU/L was associated with good outcome. In our review, although the mean duration from delivery to diagnosis was short at six weeks, high β-hCG levels were observed in most (15 patients), which may have contributed to the lower survival.

The following babies should be kept on β-hCG follow-up:

1. Babies of mothers with a history of a hydatiform mole in a previous pregnancy;
2. Babies of mothers with CC in the current or past pregnancy;
3. History of feto-maternal haemorrhage;
4. Birth of baby with severe anaemia;
5. Recurrent anaemia associated with hepatomegaly (25);
6. Haemangioma or a vascular lesion, presenting in the early months of life;
7. Any liver tumour in the baby presenting in the early months of life;
8. Any abnormality in the gross appearance of the placenta.

Equally important is screening mothers of babies with CC, mainly manifesting in the first six months of life (47). Although there are no specific and clear-cut recommendations at present (38), assuming that a majority of cases occur within six months of delivery, measurement of β-hCG every two weeks for the first six months, and monthly after that up to two years in the neonate has been recommended (5). However, it should be noted that recurrence of the disease, even long after CR (48), and secondary malignancies following chemotherapy for GTN (49), have also been reported in the literature.

Study limitations

The present systematic review provides the most recent and comprehensive overview of epidemiology, clinical manifestations, OS and prognosis in GTN co-existing in or metastatic in the mother and baby. Extensive electronic database searches were attempted to identify all globally published cases in English. However, the data were heterogeneous, and the analysis was descriptive, which are limitation of this systematic review. Case reports and series published in other languages were not included, which might be another limiting factor.

Implications for future research: This review highlights the need for more extensive research into the aetiology, progression, genetic aspects, management and long-term prognosis of cases with concurrent GTN in mother and infant.

Conclusion

The concurrent presence of GTN in the mother and baby is a rare entity and poses a diagnostic dilemma. Maternal diagnosis often follows diagnosis in the baby after an infant presents with clinical manifestations. A knowledge of the varied clinical presentation, eliciting a history of previous pregnancy loss/term pregnancy and serum β-hCG estimations are helpful for early diagnosis. GTN is a highly chemo-sensitive tumour, but the main prognostic factors determining survival are the time to diagnosis following previous pregnancy and serum β-hCG levels.

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