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Complete molar pregnancies with a coexisting fetus: Pregnancy outcomes and review of literature

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Abstract:
To review obstetric outcomes of complete hydatidiform molar pregnancies with a coexisting fetus (CHMCF), a rare clinical entity, we performed a retrospective case series of pathology-confirmed HMCF. The cases were collected via a private Maternal-Fetal Medicine physician group on social media. Each contributing institution from across the United States obtained informed consent and institutional data transfer agreements as required, then transmitted the data using a HIPAA-compliant modality. Data collected included maternal, fetal/genetic, placental and delivery characteristics. Nine institutions contributed 14 cases. We found that the median gestational age at diagnosis was 12 weeks 2 days (9w0d - 19w4d), and over half were diagnosed in the first trimester. Sixty-four percent of CHMCF cases were a product of assisted reproductive technology. Placental mass size universally enlarged over the surveillance period. When invasive testing was performed, insufficient sample or no growth was noted in 40% of the sampled cases. Antenatal complications occurred in all delivered patients. Four patients developed gestational trophoblastic neoplasia. This is the largest reported series of obstetric outcomes for CHMCF, and highlights the need to counsel patients about the severe maternal and fetal complications in continuing pregnancies, including progression to gestational trophoblastic neoplastic disease.

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Complete Molar Pregnancies with a Coexisting Fetus: Pregnancy Outcomes and Review of Literature

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Abstract

Objective To review the obstetric outcomes of complete hydatidiform molar pregnancies with a coexisting fetus (CHMCF), a rare clinical entity that is not well described.

Study Design We performed a retrospective case series with pathology-confirmed HMCF. The cases were collected via solicitation through a private Maternal-Fetal Medicine physician group on social media. Each contributing institution from across the United States (n=9) obtained written informed consent from the patients directly, obtained institutional data transfer agreements as required, and transmitted the data using a HIPAA-compliant modality. Data collected included maternal, fetal/genetic, placental and delivery characteristics. For descriptive analysis, continuous variables were reported as median with standard deviation and range.
**Results** Nine institutions contributed to the 14 cases collected. Nine (64%) cases of CHMCF were a product of assisted reproductive technology and one case was trizygotic. The median gestational age at diagnosis was 12 weeks 2 days (9w0d - 19w4d), and over half were diagnosed in the first trimester. The median hCG at diagnosis was 355,494 mIU/mL (49,770 - 700,486 mIU/mL). Placental mass size universally enlarged over the surveillance period. When invasive testing was performed, insufficient sample or no growth was noted in 40% of the sampled cases. Antenatal complications occurred in all delivered patients, with postpartum hemorrhage (71%) and hypertensive disorders of pregnancy (29%) being the most frequent outcomes. Delivery outcomes were variable. Four patients developed gestational trophoblastic neoplasia.

**Conclusion** This series is the largest report of obstetric outcomes for CHMCF to date, and highlights the need to counsel patients about the severe maternal and fetal complications in continuing pregnancies, including progression to gestational trophoblastic neoplastic disease.

**Key Points**

1) CHMCF is a rare obstetric complication and may be associated with the use of assisted reproductive technology.

2) Universally, patients with CHMCF who elected to manage expectantly developed antenatal complications.

3) The risk of developing gestational trophoblastic neoplasia after CHMCF is high, and termination of the pregnancy did not decrease this risk.

Ultrasonographic evidence of an enlarged multi-cystic placenta with a normal appearing fetus is an uncommon finding during routine surveillance of pregnancy. The differential diagnoses of
these features include partial or complete hydatidiform molar pregnancy with a co-existing fetus (HMCF), placentomal mesenchymal dysplasia (PMD), placental infarcts, chorioangioma, subchorionic hematoma, placental cysts, and placenta accreta spectrum (PAS) disorders. In the context of an otherwise normal-appearing fetus, the obstetrical course and postpartum follow-up of these conditions are vastly different (Table 1).

In the case of a complete HMCF (CHMCF), it is especially important to have an accurate diagnosis. This rare condition, affecting 20,000 to 100,000 pregnancies\textsuperscript{1,2} is fraught with potential maternal complications, such as hemorrhage, preeclampsia, and preterm delivery of the viable co-existing fetus. Persistent gestational trophoblastic neoplasia (GTN) is also seen more frequently in CHMCF, when compared to a single complete mole, and termination of the pregnancy has not been shown to decrease this risk.\textsuperscript{1,3,4}

While there have been large case series reported on CHMCF, they have focused mainly on outcomes as they relate to the GTN associated with this condition.\textsuperscript{1,3,4} In these reports, the use of artificial reproductive technology (ART) was either not reported, or when reported, did not account for a majority of cases (13%). An increased use of ART over the past several decades may affect the prevalence of CHMCF and so obstetricians should be cognizant of this condition and its associated ante-, intra- and postpartum risks. When an isolated complete molar pregnancy is noted, evacuation of the pre-malignant molar tissue is recommended. However, in the case of a CHMCF, a woman may elect to be managed expectantly to prolong the pregnancy. Here, we provide the first multi-center series of CHMCF reporting detailed accounts of the diagnosis, pregnancy outcomes, and postpartum follow-up, as well as a review of existing literature, in order to aid in the counseling of this at-risk cohort of pregnant women.
Materials and Methods

A retrospective analysis of women with CHMCF pregnancies was performed. The cases were collected via solicitation through a private Maternal-Fetal Medicine physician group on social media. Each contributing institution from across the United States (n=9) obtained written informed consent from the patient(s) directly, obtained institutional data transfer agreements as requested, and transmitted the data using a HIPAA-compliant modality.

Electronic records were reviewed and the following data were identified: maternal characteristics (age, gravidity, parity, pre-pregnancy body mass index, race and prior maternal co-morbidities), mode of conception, gestational age at diagnosis, human chorionic gonadotropin (hCG) at diagnosis, zygosity of the pregnancy, screening assessments (including laboratory and imaging), antenatal genetics (procedure type, results and timing), and size of placental mass as measured by prenatal ultrasonography. Maternal complications including vaginal bleeding, hyperthyroidism, and hypertensive disorders of pregnancy were noted. The timing, mode and indication for delivery, as well as the estimated blood loss or complications of delivery or procedure were recorded. Postnatal confirmation of genetics and pathology, postpartum follow-up, including hCG trend and time to nadir, diagnosis of GTN and subsequent treatments were identified.

Fetal and neonatal outcomes recorded included any structural anomalies noted prenatally, intrauterine fetal growth restriction, intrauterine or neonatal fetal demise, and neonatal birthweight.

Statistical Analysis

For descriptive analysis, continuous variables were reported as median with standard deviation and range. Categorical variables were reported as proportions.
Results

After solicitation via social media, nine institutions were able to obtain patient consent and contributed 14 cases in total. Clinical characteristics of the patients are delineated in Table 2.

Of the cases presented here, 64% were the product of ART: 29% ovulation induction alone, 21% ovulation induction with intrauterine insemination, and 14% in-vitro fertilization. Only five cases (36%) were due to spontaneous conception. The median gestational age at diagnosis was 12w2d (9w0d-19w4d), with 64% (n=9) diagnosed in the first trimester and the remaining diagnosed by 20 weeks gestation. Upon either diagnosis or suspicion of diagnosis, all patients were referred to a Maternal-Fetal Medicine specialist, who was involved in the remainder of the pregnancy. The median hCG at diagnosis was 355,494 mIU/mL (49,770-700,486 mIU/mL). The largest dimension of the placental mass at time of diagnosis varied, ranging from 3.5-12 cm. The size of the placental mass universally enlarged over the antenatal surveillance period. Antenatal genetic analysis was performed in ten of the fourteen cases. Insufficient sample or no growth of the sample from either amniocentesis (n=5) or chorionic villous sampling (CVS) (n=5) was a common finding, occurring in 40% of cases sampled (n=4).

In the reported dizygotic CHMCF pregnancies, no malformations were identified. The one case of trizygotic CHMCF pregnancy had a complete mole, a co-existing structurally normal fetus, and a partial molar pregnancy with cystic hygroma and complex congenital heart defect.

Antenatal management and complications are described in Table 3. Universally, patients with CHMCF experienced some form of antenatal complication, including vaginal bleeding (10; 71%), hypertensive disorder of pregnancy (4; 28.9%), pulmonary edema (1; 0.7%) and hyperthyroidism (1; 0.7%). Of the patients with vaginal bleeding, 4 out of 10 (40%) required
admission and/or transfusion. The case of hyperthyroidism required medical treatment with antithyroid medications and ultimately resulted in termination of pregnancy.

The majority of patients opted for expectant management (64.3%, n=9), and the average GA at delivery was 28w3d (16w6d to 34w5d). One patient developed an early-onset HELLP-like syndrome at 16w6d which prompted treatment with D&E. Another patient experienced persistent vaginal bleeding throughout the pregnancy, resulting in preterm labor and vaginal delivery at 20w2d. A third patient developed hemorrhage and chorioamnionitis and was delivered at 17w5d. Two patients who opted for expectant management also had postpartum hemorrhage, with one of these requiring a hysterectomy due to bleeding after emergent delivery at 24w5d. She subsequently required treatment for metastatic GTN. (Table 3)

None of the patients who opted for termination of pregnancy had complications from the procedure, including hemorrhage (Table 3). One of the patients who underwent termination of pregnancy developed pulmonary edema at 20w0d at time of diagnosis.

GTN was diagnosed in 28.6% of patients (n=4), with two (2/8; 25%) from the expectant management group and two (2/5; 40%) from the termination group. The two cases of GTN from the termination group were FIGO Stage 1 and 3, while the two cases from the expectant management were FIGO Stage 3 and 4. All were treated with IV methotrexate. One patient also received leucovorin, and the patient with FIGO stage 4 disease also received IV dactinomycin. Two of these patients also were noted to have a nadir in their hCG levels by Day 56 post-delivery evacuation.

**Discussion**
In this series we analyzed the patient characteristics, diagnosis, pregnancy complications and resultant obstetric outcomes of 14 pregnancies complicated by CHMCF. Complete hydatidiform moles (CHM) are generally homozygous 46, XX and result from duplication of the haploid genome of a single sperm following fertilization of an ovum in which the maternal chromosomes are lost during meiosis, or due to postzygotic diploidization in a triploid conception. A multizygotic pregnancy consisting of a partial or complete HMCF is a rare complication of pregnancy, and the available cases series to date focus on GTN risk, instead of obstetrical risk. A multi-cystic placental mass on ultrasound imaging is typically seen in the first trimester (Figures 1-4 and Supplementary video) and should trigger a referral to a Maternal-Fetal Medicine specialist for further imaging and potential diagnostic testing. With improved ultrasound technology and rising rates of ART, HMCF diagnoses may be made earlier and more frequently, highlighting the importance of data accrual on the course and outcome of these pregnancies.

The differential diagnosis of a multi-cystic placenta with a co-existing fetus can be broad, as a multi-cystic placenta can represent a hydropic abortus, chromosomal abnormalities, digynic triploid conceptions, placental mesenchymal dysplasia or a molar pregnancy. These distinct diagnoses have varying complications, potential outcomes and management strategies. The ability to differentiate between these diagnoses is key for optimal counseling and management. Pregnancies with these sonographic findings should be evaluated by and co-managed with a Maternal-Fetal Medicine subspecialist. Maternal serum alpha-fetoprotein (AFP) measurements and beta hCG measurements are helpful in confirming the diagnosis. The levels in our case series are comparable to previous case series with beta hCG levels greater than 150,000 mIU/mL. Previous cases series have suggested a plateau of beta hCG levels in the second trimester and
that a failure to reach a plateau was associated with increased risk of adverse pregnancy outcomes.\textsuperscript{7}

Ultrasound, beta hCG and MSAFP may not provide sufficient data to differentiate between possible diagnoses; thus, invasive diagnostic testing may be necessary for genetic analysis. Amniocentesis can be utilized to evaluate for a triploidy in the co-existent fetus or the placenta as this would be suggestive of a partial hydatidiform mole. Previous literature has suggested CVS of the suspected molar tissue as an alternative via molecular genotyping and segregation analysis of paternal and placental alleles, as absence of maternal alleles can confirm a diandrogenic complete mole.\textsuperscript{9-11} Our series is the first to report common use of invasive testing in CHMCF, and to show that 40\% of invasive procedures may yield no growth or insufficient sample in these cases. Pre-procedural counseling regarding invasive testing should include this potential outcome of testing.

Furthermore, CHM is well recognized to have the potential for local invasion and distant spread. It has also been suggested that persistent trophoblastic disease and metastatic GTN are more pervasive with a multifetal gestation with concurrent mole, up to 30\% increased risk.\textsuperscript{12} Beta hCG and molar volumes have been used to predict malignant potential, although this is an area where more research is needed.\textsuperscript{12}

The presence of a CHMCF creates complications for both the mother and the fetus with the clinical course frequently complicated by vaginal bleeding, preeclampsia, hyperemesis gravidarum, hyperthyroidism and gestational trophoblastic disease.\textsuperscript{10} Our case series describes the complications rates in a modern cohort, particularly highlighting the significance of morbid vaginal bleeding and hypertensive disorders of pregnancy in these women. A recent systemic review reported similar findings of a high rate of perinatal morbidities.\textsuperscript{13}
Including the cases reported in this series, sixteen reports of trizygotic pregnancy with two co-existing fetuses and a complete mole have been reported (Table 4). Of the 16 cases, 87.5% have been pregnancies conceived with ovulation induction medications. The clinical course of these pregnancies shows that vaginal bleeding is very common, presenting in 59% of the cases reported to date.

The risk of GTN is higher in the presence of a complete mole compared to a partial mole (14-20% compared to 1-5%). GTN can include invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor. The series reported here suggests that the incidence of GTN may be higher in CHMCF than in other molar pregnancies, with 28.6% of patients in this series having GTN. Although the group who opted for termination had a high percentage of GTN, the FIGO stages appeared to be lower. This highlights the importance of counseling regarding the risk of distant metastatic disease with expectant management and need for close patient follow-up post-delivery of patients with CHMCF.

A recent meta-analysis by Albright et al. states that the risk of GTN in patients with normalization of beta HCG by day 56, or after 8 weeks, is 0.35% for complete mole and 0.03% for partial mole. This is in contrast to our series, where 50% of CHMCF patients who developed GTN had a nadir of beta hCG by day 56. More studies and collaborative efforts are warranted to further evaluate the possibility of additional risk of GTN. It is well known that CHMCF carries a much greater risk of pregnancy complication if expectant management is carried out, with increased risk of vaginal bleeding, preeclampsia and preterm labor, but the increased risk of CHMCF may also carry a significantly increased risk of GTN, and this may indicate a longer period of serial beta hCG measurements and surveillance and should prompt extensive patient counseling.
One of the greatest strengths of our study is that it is the largest series to date for obstetric data in CHMCF and includes a wide geographic region. Additionally, the use of social media to engage physicians from across the country is a novel approach to transmural collaborations, instead of individual reports of complex cases. Once connected, the physicians were able to use a standardized collection of data across institutions, giving more uniformity to the data for comparison. While our study has many strengths, it is limited by the potential of selection bias, and given its retrospective recall of cases, the worst cases with the poorest outcomes could have been collected and reviewed. Furthermore, the observational nature of the study cannot truly compare the management protocols, as is often the case with rare disorders.

Overall, our findings demonstrate that it is possible to manage CHMCF expectantly but requires shared decision-making while factoring in maternal antepartum and peripartum risks, as well as increased risk of subsequent metastatic GTN. This case series can serve as a tool for engaging in full counseling of patients about the varied and potentially significant outcomes of CHMCF gestations which are likely to be on the rise with the increasing use of ART.

Additionally, it is also important to consider innovative methods of extramural collaboration to amplify data accrual for rare disorders, such as CHMCF. This case series demonstrates a novel collaboration, as the idea was initiated in a private social media group of physicians and resulted in a wide collaborative effort from institutions across the United States. These same methods can be used with other rare complications to expand our knowledge base and lead to more meaningful observations from which to draw conclusions.
Table 1: Comparison of the clinical findings of placental mesenchymal dysplasia (PMD), complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM)

|                      | PMD                                                        | CHM                                                        | PHM                                                        |
|----------------------|------------------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------|
| Ultrasound findings  | Enlarged multi-cystic placenta with anechoic regions ("moth-eaten" appearance) | Findings widely distributed, large edematous villi          |                                                            |
| Fetus\(^{18}\)        | • Can be unremarkable                                      | • Co-existing fetus can be unremarkable                     | • May be structurally abnormal triploid fetus\(^{19}\)       |
|                      | • FGR (50%)                                                |                                                            |                                                            |
|                      | • IUFD or neonatal death (43%)                             |                                                            |                                                            |
|                      | • Consider BWS findings: macroglossia, omphalocele, genitourinary abnormalities, overgrowth, polyhydramnios |                                                            |                                                            |
| Pathology            | • Enlarged stem villi with loose                           | • Hydropic swelling of villi                               | • Focal trophoblastic hyperplasia                           |

\(^{18}\) FGR: Fetal growth restriction; IUFD: Intrauterine fetal death; BWS: Beckwith-Wiedemann syndrome.
| Connective Tissue and Cistern-like Formations | Diffuse Trophoblastic Hyperplasia | Marked Variability in the Size and Degree of Swelling, and Cavitation of the Villi |
|-------------------------------------------|----------------------------------|----------------------------------------------------------------------------------|
| • Absent Trophoblastic Changes            | • Diffuse and Marked Trophoblastic Atypia at the Molar Implantation Site | • Marked Scalloping and Prominent Stromal Trophoblastic Inclusion in the Villi |
|                                           | • Focal and Mild Trophoblastic Atypia at Molar Implantation Site       | • Focal and Mild Trophoblastic Atypia at Molar Implantation Site |

**Associated Maternal Morbidities**

| None Identified | GTN | 1. GTN |
|-----------------|-----|--------|
|                 | Preeclampsia | 2. Preeclampsia |
|                 | Choriocarcinoma | 3. Choriocarcinoma |

**Cytogenetics**

| Normal Karyotype (89%) | 46 XX: Haploid 23 X Sperm Duplicates Its Own Chromosomes | Triploidy: Extra Haploid Sperm |
|------------------------|----------------------------------------------------------|-------------------------------|
| 46 XX (78%), 46 XY (22%) | • 46 XY: Ova Penetrated by 2 Sperm (Dispermy), 46 XY | |
| BWS- Confirmed or Suspected (23%) | | |

**Clinical**

| No Definitive Clinical | Vaginal Bleeding | Commonly |
|------------------------|------------------|----------|
presentation characteristics, but may be associated with preterm labor, secondary to amniotic fluid abnormalities

- Size greater than dates
- Theca lutein cysts
- Hyperemesis
- Preeclampsia
- Hyperthyroidism
- Pulmonary edema
- Respiratory distress

diagnosed after missed or incomplete abortion, based on pathology

BWS Beckwith-Wiedemann syndrome; CHM complete hydatidiform mole; FGR fetal growth restriction; IUFD intrauterine fetal demise; PHM partial hydatidiform mole; PMD placental mesenchymal dysplasia; GTN gestational trophoblastic neoplasia

Table 2. Patient characteristics and comorbidities

| Case # | Age | G/P | Conception | BMI | Race/Ethnicity | Co-Morbidities          |
|--------|-----|-----|------------|-----|---------------|-------------------------|
| 1      | 30  | 2/1001 | OI/GnTP/IUI | 20.8 | Caucasian     | None                    |
| 2      | 27  | 1/0   | OI/CC      | 26.7 | Caucasian     | PCOS, Seizure disorder on Lamictal |
| 3      | 36  | 1/0   | OI/CC/IUI  | 30.6 | Caucasian     | Lupus on Plaquenil     |
| 4      | 32  | 2/1001 | Spontaneous | 23.0 | Caucasian     | None                    |
| 5      | 26  | 2/0010 | Spontaneous | 34.0 | Caucasian/Asian | Anxiety, Depression   |
| 6      | 29  | 2/1001 | OI/GnTP    | 22.6 | Caucasian     | Chronic Hypertension   |
| 7      | 27  | 1/0   | OI/CC      | 36.0 | Caucasian     | None                    |
| Case# | Planned Management | Complications | GA at Delivery | Delivery Type | EBL (mL) | Genetics Prenatal | hCG Trend | Subsequent Dx |
|-------|--------------------|---------------|----------------|---------------|----------|-------------------|-----------|----------------|
| 1     | Expectant (initially declined termination) | Serial growth | SAB of Twin B at 14w, HELLP at 16w | D&E | 16w6d | 1000 | 70 XXXY | Plateau at 8w PP, Metastatic GTN (FIGO Stage 3), Lung Nodules |
| 2     | Spontaneous | 31.6 | White | h/o Roux-en-Y, Anemia, h/o gestational HTN |
| 3     | Spontaneous | 28.2 | White | Migraine, PCOS with infertility |
| 4     | Spontaneous | 19.4 | Arab-American | h/o 2nd trimester IUFD (19w) |
| 5     | Spontaneous | 21.0 | White | h/o bilateral PE, h/o 2nd trimester IUFD (16w) |
| 6     | IVF | 22.9 | Asian | seizures on levetiracetam and lamotrigine |
| 7     | COH/IUI | 24.0 | Caucasian | None |
| 8     | IVF | 21.0 | Asian | Asthma |

BMI body mass index; CC clomiphene citrate; COH controlled ovarian hyperstimulation; GnTP gonadotropin; h/o history of; HTN hypertension; IUI intrauterine insemination; IUFD intrauterine fetal demise; IVF in-vitro fertilization; OI ovulation induction; PCOS polycystic ovarian syndrome; PE pulmonary embolism

Table 3. Antenatal Management and Pregnancy Outcomes
| Ultrasounds Termination when HELLP | 2 | Expectant (declined termination) | VB (admission) | 20w2d | SVD | 300 | None | Nadir by 12w PP | None |
|-----------------------------------|---|----------------------------------|---------------|-------|-----|-----|------|-----------------|------|
| Serial growth Ultrasounds         | 3 | Expectant VB                     | 13w3d         | D&E   | 200 | T22 | Nadir by 13w PP | None |
|                                   | 4 | Expectant (declined termination) | VB Hyperthyroidism (admission) | 24w5d | Emergent Classical CD | 2500 | None | Nadir by 8w PP then increased | Metastatic GTN FIGO Stage 4 |
|                                   |   | Anemia                           |               |       |     |     |                  |      |
|                                   |   | Tachycardia                       |               |       |     |     |                  |      |
|                                   |   | Palpitations                      |               |       |     |     |                  |      |
|                                   |   | Preterm labor                     |               |       |     |     |                  |      |
|                                   |   | Anemia/transfusion (2U pRBC)      |               |       |     |     |                  |      |
|                                   |   | PEC with severe features          |               |       |     |     |                  |      |
|                                   |   | Hemorrhage with passage of molar tissue |     |       |     |     |                  |      |
|                                   |   | Intraoperative transfusion (3U |               |       |     |     |                  |      |
| Case | Action | Indication | Week | Procedure | Blood Loss | Outcome | Notes |
|------|--------|------------|------|-----------|------------|---------|-------|
| 5    | Desired termination | Pulmonary edema due to Postpartum hemorrhage | 21w1d | D&E | 125 | None | Nadir by 7w PP |
| 6    | Expectant | SAB of Twin A VB | 34w5d | SVD | 250 | None | Nadir by 4w PP |
| 7    | Expectant | VB GHTN | 34w2d | Classical CD | 1000 | None | Not available |
| 8    | Expectant | VB and anemia PTL Postpartum hemorrhage | 32w2d | Urgent classical CD due to funic presentation | 1500 | None | Nadir by 7w PP |
| 9    | Expectant | VB | 28w3d | SVD | 350 | None | Nadir by 10w |
|   | Serial labs | PTL | HTN | Fever and tachycardia (unclear diagnosis) |   | PTL | HTN | Fever and tachycardia (unclear diagnosis) |   | PTL | HTN | Fever and tachycardia (unclear diagnosis) |   | PTL | HTN | Fever and tachycardia (unclear diagnosis) |
|---|-------------|-----|-----|------------------------------------------|---|-----|-----|------------------------------------------|---|-----|-----|------------------------------------------|---|-----|-----|------------------------------------------|
| 10 | Desired termination | Abnormal TFTs with palpitations (started Methimazole) Bilateral ovarian masses (largest 10x9x8 cm) | 15w0d | D&E | 250 | None | Nadir by 4w PP then elevated Metastatic GTN FIGO Stage 3 |   |   |   |   |
| 11 | Expectant termination | VB | PTL | 34w2d | SVD | 300 | None | Nadir by 6w PP None |   |   |   |   |
| 12 | Desired termination | VB | 16w6d | D&E | 250 | None | Nadir by 12w PP None |   |   |   |   |
| 13 | Desired termination | None | 15w0d | D&C | 50 | None | Plateau at 2w PP GTN FIGO Stage 1 |   |   |   |   |
| 14 | Expectant | Chorioamnionitis | 17w5d | SVD | 500 | 46 XX | Nadir by 12w None |   |   |   |   |
GA gestational age; CD cesarean delivery; D&C dilation and curettage; D&E dilation and evacuation; FIGO International Federation of Gynecology and Obstetrics; GTD gestational trophoblastic disease; GTN gestational hypertension; HELLP hemolysis, elevated liver enzymes, low platelets; HTN hypertension; IV intravenous; MTX methotrexate; PTL preterm labor; PP postpartum; SAB spontaneous abortion; SVD spontaneous vaginal delivery; VB vaginal bleeding; PRBCs packed red blood cells

Table 4: Cases of trizygotic pregnancies consisting of complete mole and two co-existing twins

| Reference | Age (y) | Conceptio n | GA at deliver y (weeks) | Maternal Complication s | Pregnancy Outcome | GTD | Postpartum Therapy | Confirmation of diagnosis |
|-----------|---------|-------------|-------------------------|------------------------|------------------|-----|---------------------|--------------------------|
| Sauerbrei 1990<sup>14</sup> | 23      | Clomiphe ne 22 | VB, PEC with severe features at 22 weeks | Spontaneous abortion | No | MTX, ActD (5 cycles) | Postpartum pathology |
| Ohmichi 1986<sup>15</sup>  | 34      | hMG-hCG 17 | VB | Spontaneous abortion | PTT | N/A | Postpartum pathology |
| Azuma    24      | hMG-hCG 19 | VB | Spontaneous | No | N/A | Postpartum pathology |
| Year   | Case  | Methodology | Age | Type   | Results                        | Treatment                  | Notes                           |
|--------|-------|-------------|-----|--------|--------------------------------|----------------------------|--------------------------------|
| 1992   | 24    | VB          |     | Abortion| Pathology                     | Antepartum US findings and elevated hCG confirmed |  
| 1992   | 24    | GIFT        | 31  | Abortion| Pathology                     | Antepartum US findings and elevated hCG confirmed |  
| 1997   | 17    | Hyperthyroidism, hyperemesis |     | Induced abortion due to hyperemesis | Choriocarcinoma, pulmonary metastasis | MTX (2 cycles) |  
| 1998   | 15    | VB          | 31  | Induced abortion due to VB      | Invasive mole               | MTX, ActD (6 cycles) |  
| 1999   | 22    | Hyperthyroidism, PEC with severe features, pulmonary |     | Induced abortion due to maternal status | Invasive mole               | MTX (7 cycles), Etoposide (2 cycles) |
|                | Age | Treatment | GA | Edema | Induction | Diagnosis                                      | Follow-Up | Outcome                          |
|----------------|-----|-----------|----|--------|-----------|-----------------------------------------------|-----------|----------------------------------|
| Gray-Henry 1999 | 31  | Metrodin, hCG | 16 | Massive VB | Induced abortion due to life-threatening hemorrhage | No  | N/A  | Antepartum US findings and elevated hCG, Confirmed postpartum |
| Amr 2000       | 31  | Clomiphenene, hCG | 30 | None | PTL, SVD, neonatal death of 1 twin | No | N/A | Postpartum placental pathology |
| Rajesh 2000    | 29  | Spontaneous | 24 | VB | PTL, SVD, neonatal death of both twins | No | N/A | Antepartum US findings and elevated hCG, Confirmed postpartum |
| Malhotra 2001  | 29  | Spontaneous | 21 | VB | Spontaneous abortion | No | N/A | Antepartum placental pathology, Confirmed postpartum |
| Takagi 2003    | 37  | hMG, hCG | 28 | Cerclage placed | PTL, CD for malpresentation, survival of both twins | Invasive mole, pulmonary metastases | MTX (6 cycles) | Antepartum placental pathology, Confirmed postpartum |
| Bovicelli      | 32  | ICSI      | 31 | VB | Emergency | No | N/A | Antepartum US findings and elevated hCG, Confirmed postpartum |
| Year | Case Description | Causes of Death | Antepartum US Findings | Elevation of hCG | Postpartum Findings |
|------|------------------|------------------|------------------------|-----------------|-------------------|
| 2004 | CD for non-reassuring fetal testing, IUFD of one twin (fetomaternal hemorrhage) | elevated hCG, CVS c/w all paternal genotype | | | Confirmed postpartum |
| 2004 | Steigrad 40 | IVF | VB | 34 | CD due to VB, survival of both twins, Metastatic GTN, pulmonary metastases | MTX, FA (3 cycles) | Antepartum elevated hCG, Confirmed postpartum |
| 2007 | Ko 36 | IVF-ET, donor embryo | PEC with severe features | 33 | CD due to PEC, survival of both twins | No | Antepartum elevated hCG, Confirmed postpartum |
| Present report | 30 | GnTp, IUI | 16 | HELLP | SAB of Twin B, then induced abortion of Twin A due to maternal status | Metastatic GTN, pulmonary metastases | MTX | Antepartum elevated hCG, Confirmed unremarkable mole |
|----------------|----|-----------|----|--------|---------------------------------|----------------------------------|-----|---------------------------------------------------|

ActD actinomycin D; CD cesarean delivery; EMA-CO etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine; ET embryo transfer; FA folinic acid; GA gestational age; GIFT gamete intrafallopian transfer; GTD gestational trophoblastic disease; GTN gestational trophoblastic neoplasia; hCG human chorionic gonadotropin; HELLP hemolysis elevated liver enzymes low platelets syndrome; hFSH human follicle stimulating hormone; hMG human menopausal gonadotropin; ICSI intracytoplasmic spermatic injection; IUFD intrauterine fetal demise; IUI intrauterine injection; IVF in vitro fertilization; MTX methotrexate; PEC preeclampsia; PT preterm PTL preterm labor; SVD spontaneous vaginal delivery; VB vaginal bleeding

Figure 1 Dizygotic pregnancy with large complete hydatidiform molar tissue and normal placenta.

Figure 2 Dizygotic pregnancy at 11 weeks 4 days with complete hydatidiform molar tissue and viable fetus.
Figure 3 Dizygotic pregnancy with complete hydatidiform molar tissue and abutting normal placenta from a viable fetus.

Figure 4 Trizygotic pregnancy at (a) 11 weeks 5 days with complete hydatidiform molar tissue, (b) 24 weeks with head of Twin B and complete hydatidiform molar tissue.

**Supplementary video**

Dizygotic pregnancy with complete hydatidiform molar tissue and a viable fetus with normal placental tissue.

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