

Is a Complete Hydatidiform Mole and a Co-existing Normal Fetus an Iatrogenic Effect?

Nataly Zilberman Sharon MD^{1,2}, Yaakov Melcer MD^{1,2} and Ron Maymon MD^{1,2}

¹Department of Obstetrics and Gynecology, Shamir Medical Center (Assaf Harofeh), Zerifin, Israel

²Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Complete hydatidiform mole and a co-existing normal fetus (CHMCF) is associated with a high complication rate. A possible association with assisted conception might increase the prevalence of CHMCF.

Objectives: To study the potential association between assisted conception and the risks of CHMCF.

Methods: Case series at a single university hospital from 2008 to 2018 are presented and contrasted with data from a comprehensive literature review (1998–2018). Cases were identified from the institutional database that matched the sonographic criteria for CHMCF. A literature review showed comparable cases.

Results: None of the three pregnancies presented in this article resulted in a viable fetus, all were aborted. One of the three patients needed chemotherapy due to gestational trophoblastic neoplasia (GTN). A literature search identified 248 reported cases in which 22 fetuses (9%) reached term, 88/248 (35%) progressed to GTN, and 25/120 (21%) were conceived following assisted conception. From 2008 until 2018 at our medical facility, there were 3144 twin pregnancies of which 1667 (53%) were conceived using assisted conception. In our cohort, there was no statistical trend for assisted conception as an etiological factor for CHMCF.

Conclusions: No association between assisted conception and the risk for CHMCF was established at our hospital, although approximately one-quarter of all reported CHMCF pregnancies are attributed to assisted conception technology. However, these data are not always reported, making it difficult to draw definitive conclusions.

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KEY WORDS: assisted conception, complete hydatidiform mole, pregnancy outcome, twins, ultrasound complete hydatidiform mole and a co-existing normal fetus (CHMCF)

Twin pregnancies account for 3% of all live births [1] and are complicated by high rates of preterm delivery, growth restriction, congenital anomalies, and infant mortality [2,3]. Approximately 30% of twin pregnancies are attributed to assisted reproduction techniques [4]. These pregnancies can be further complicated by a complete hydatidiform or partial hydatidiform

mole. Multiple gestation with a complete hydatidiform mole and a co-existing normal fetus (CHMCF) is nevertheless a very rare event, with an estimated incidence of one in 20,000–100,000 pregnancies [5-7]. A complete hydatidiform mole can co-exist with a potentially viable fetus and a normal placenta, whereas a partial mole consists of a non-viable triploid conceptus and an abnormal placenta [8]. This difference is crucial because a complete hydatidiform mole poses a considerable risk for gestational trophoblastic neoplasia (GTN), whereas the risk of a partial mole progressing to GTN is less than 5% [9]. In addition to the risk of neoplasia, a CHMCF can lead to early and severe onset preeclampsia, intrauterine fetal demise (IUGR), preterm labor, and hemorrhage [7,10,11].

Emerging evidence suggests that conservative management of CHMCF may not increase the risk of GTN [5,11,12]. Nevertheless, the general policy is to advise termination of pregnancy given the high risks of these pregnancies.

Although some studies have pointed to an association between CHMCF and fertility treatments, there is little clinical data to confirm this supposition. Despite all ovulation stimulation techniques increase the rate of twin pregnancies, what causes the higher risk of CHMCF remains unclear [13-16]. This article reviews recent data on CHMCF and presents three case studies from our hospital, to better understand its potential relationship to assisted conception.

PATIENTS AND METHODS

The medical records of all pregnant women expecting twins who had been diagnosed and treated in our department from 2008 to 2018 were collected and reviewed. Of these, three women were diagnosed with CHMCF. These cases were detected during routine sonographic evaluations conducted by experienced sonographers. All three women fulfilled our criteria for sonographic diagnosis of CHMCF: a heterogeneous mass with numerous discrete anechoic spaces, a co-existing separate gestational sac with a normal fetus, and +/- ovarian theca lutein cysts.

LITERATURE REVIEW

The literature review was conducted by searching in the Medline and PubMed databases for cohort studies or case

series related to CHMCF. We used the following MeSH (Medical Subject Headings) terms: “Gestational Trophoblastic Disease” OR “Hydatidiform Mole” AND “Pregnancy, Twin” OR “Multiple, Pregnancy”. Only studies in English consisting of at least three or more cases published between 1998 and 2018 including data on clinical presentation, pregnancy outcomes and GTN progression were included [Table 1].

The average gestational age at diagnosis was 14 weeks gestation, and the median maternal serum of the beta human chorionic gonadotropin (bhCG) at diagnosis was 553,704 mIU/ml. Maternal complications ranged from 4 to 100%, although the actual complication rate that led to induced abortion was 4–71%. This high variability may be related to differences in defining vaginal bleeding as a complication, as some publications mention all vaginal bleeding while others only life-threatening hemorrhage. Preeclampsia occurred at a rate of 0–35% in the CHMCF cases identified. Hyperthyroidism was seldom mentioned.

Delivery of a viable fetus occurred in 14.3–71% of CHMCF pregnancies, with 12% achieving full-term pregnancy. The GTN rate was between 14–57%, with several articles demonstrating no correlation between the pregnancy length and the rate of progression to GTN [10,11]. Of the 248 reported cases,

information about mode of conception was available for 120 cases. Of these, 25 (21%) were conceived using assisted conception technology.

This literature overview formed the basis for our detailed examination of the three case studies we found in our hospital records from 2008 to 2018 [Table 1].

RESULTS

CASE STUDIES

General profile

From 2008 to 2018, the prevalence of twin pregnancies in our hospital was 3144, of which 1667 (53%) were conceived using assisted conception. In our cohort, because of the small number of the cases, statistical trends for assisted conception could not be calculated as an etiological factor for CHMCF. The clinical data of the three patients are presented in Table 2. The mean maternal age was 30.7 years (range 25–41) with a gravidity of 1 to 3. The mean gestational age at diagnosis was 11.3 weeks (range 10–16). The mean maternal serum bhCG level at diagnosis was 1,550,343 mIU/ml. Two were conceived using assisted conception and one spontaneously. All three

Table 1. Summary of publications on multiple gestations with a complete hydatidiform mole and co-existing normal fetus

Author and reference number	Year	Number of cases	Assisted conception	bHCG	GA at diagnosis	Mean maternal age (range)	Overall maternal complication	Bleeding	Hyperthyroidism	PET	Elective abortion	Medically induced abortion	SA/IUFD	Delivery of viable infant	Term delivery	GTN
Fishman et al. [19]	1998	7	0	NK	NK	27	5 (71%)	NK	NK	NK	0	5 (71%)	NK	2/7 (28%)	0	4 (57%)
Matsui et al. [10]	2000	18	NK	NK	NK	29 (21–37)	8 (44%)	3 (17%)	0	5 (28%)	5 (28%)	8 (44%)	2 (11%)	3/13 (23%)	2 (11%)	9 (50%)
Sebire et al. [22]	2002	77	NK	NK	NK	NK	3 (3.9%)	0	0	3 (3.9%)	24 (31%)	2 (2.6%)	31 (40.3%)	20/77 (25.9%)	NK	15 (19.4%)
Wee and Jauniaux [8]	2005	8	NK	NK	14+/-4	NK	8 (100%)	8 (100%)	0	1 (12%)	1 (12%)	0	2 (25%)	5/7 (71%)	3 (37%)	3 (37%)
Massardier et al. [13]	2009	14	4 (29%)	NK	NK	30 (21–43)	9 (64.3%)	3 (21.4%)	4 (28.6%)	4 (28.6%)	3 (21.4%)	5 (35.7%)	3 (21.4%)	3 (21.4%)	1 (7%)	7 (50%)
Lee et al. [20]	2010	6	4 (67%)	582,552	12.6	31 (26–39)	4 (67%)	2 (33.3%)	4 (67%)	2 (33.3%)	1 (16.7%)	2 (33.3%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	3 (50%)
Kihara et al. [17]	2012	17	NK	NK	14.9+/- 5.7	32 (22–40)	6 (35%)	NK	NK	6 (35%)	2 (12%)	1 (0.6%)	9 (52.9%)	5/17 (29.4%)	4 (23.5%)	8 (47%)
Kutuk et al. [18]	2014	7	2 (29%)	141,720	16.1+/-4.6	25 (23–29)	2 (28%)	2 (28%)	0	0	2 (28%)	0	4 (57%)	1/7 (14.3%)	0	1 (14.3%)
Lin et al. [11]	2017	70	9 (13%)	400,000	15	28* (18–41)	41 (58.5%)	36 (51.4%)	20 (28.6%)	7 (10%)	10 (14.3%)	7 (10%)	17 (24.3%)	36/70 (51.4%)	11 (15.7%)	31 (44.3%)
Current review	2018	3	2 (67%)	1,298,000	12.6	31 (25–41)	2 (67%)	2 (67%)	0	1 (33%)	1 (33%)	2 (67%)	0	0	0	1 (33%)
Total number of cases		248		553,704	14.5	29 (18–43)	105 (42%)	71 (29%)	30 (12%)	29 (12%)	56 (23%)	32 (13%)	77 (31%)	82 (33%)	22 (9%)	88 (35%)
Total known mode of conception		120	25 (21%)												0	

*only median available

beta human chorionic gonadotropin (bhCG), GA = gestational age, GTN = gestational trophoblastic neoplasia, IUFD = intrauterine fetal demise, PET = preeclamptic toxemia, SA = spontaneous abortion

Table 2. Data on the three cases of complete hydatidiform mole and a co-existing normal fetus in our department

Patient number	Age (years)	Gravidity	Parity	GA at diagnosis	Previous mole	Maternal serum bhCG levels at diagnosis (mIU/ml)	GA at termination	Emergency induced abortion due to medical condition	Induced abortion	Maternal complications	PET	Bleeding	IUFD	Assisted conception	Viable fetus delivery
1	41	3	1	10.2	0	353,029	14	0	1	0	0	0	0	1	0
2	25	1	0	11.4	0	1,298,000	11.5	0	1	1	0	1	0	1	0
3	26	1	0	12.3	0	3,000,000	14	1	0	1	1	1	0	0	0
Mean	30.7			11.3		1,550,343		2	2	3	2	2	0	3	0

beta human chorionic gonadotropin (bhCG) m GA = gestational age, IUFD = intrauterine fetal demise, PET = preeclampsic toxemia

women had induced abortions, two because of sudden medical complications and one electively. The average gestational age at termination of pregnancy was 13 weeks (range 11–14).

Two of the women presented with vaginal bleeding and one with preeclampsia. Vaginal hemorrhage was defined as excessive vaginal bleeding leading to hospitalization, hemodynamic instability, blood transfusion, or urgent induced abortion. Preeclampsia was defined as hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) associated with proteinuria on a dipstick or at least 300 mg in 24 hours. None of the women in our series presented with clinical hyperthyroidism or respiratory distress

After termination of pregnancy, the weekly serum hCG of each patient was monitored until undetected values were reached, and then up to 6 months. One patient needed complementary chemotherapy [Table 2].

Case 1

A 41-year-old, gravida 3, para 1 presented for evaluation of a uterine mass at 10.2 weeks of gestation. The mass was first seen in at 7.2 weeks of gestation and was suspected to be a hematoma. The pregnancy was conceived through in vitro fertilization (IVF) sperm donation, and two fetuses were observed. No relevant maternal history was identified. The patient mentioned more vomiting and nausea than her previous pregnancies. bhCG was 353,029 mIU/ml. On the ultrasound scan, a gestational sac with a viable appropriate fetus was identified. Next to it was a multi-cystic mass. The ovaries appeared normal on an ultrasound scan. One week later, the bhCG rose to 555,829 mIU/ml, and the sonographic scan confirmed a complete mole with a co-existent normal fetus. She was informed about the possible complications and was advised to terminate the pregnancy. The woman asked for a second opinion, which recommended the same treatment, and she therefore chose to terminate her pregnancy at 14 weeks of gestation.

Case 2

A 27-year-old gravida 1, para 0 pregnant with bichorionic diamniotic twins first presented at our emergency department with vaginal bleeding at 8.5 weeks of gestation. She conceived

by ovulation induction due to polycystic ovary syndrome. No other relevant maternal history was identified. Physical examination revealed remnants of vaginal bleeding. On a sonographic scan, two viable appropriate fetuses were identified. At 11.2 weeks of gestation she was referred to our department with a diagnosis of a molar pregnancy. bhCG was measured 1,298,000 mIU/ml. On the sonographic scan two viably appropriate fetuses were seen, with a multi-cystic thick mass next to them. The woman was informed about the possible complications and chose to terminate the pregnancy. bhCG levels remained elevated during follow-up, and therefore she received additional treatment with methotrexate.

Case 3

A 26-year-old gravida 1, para 0 presented to our emergency department at 12.3 weeks of gestation with recurrent vaginal bleeding and excessive vomiting. Vital signs showed elevated blood pressure of 140/85 mmHg. Physical examination showed a uterus matching a gestational age of 18 weeks and remarkable leg edema. bhCG was measured 3,000,000 mIU/ml. Lab results showed elevated liver enzymes. The sonographic scan showed a uterine sac containing a multi-cystic mass and a viable crown–rump length-appropriate fetus next to it. She was advised to terminate the pregnancy due to evident preeclampsia and CHMCF diagnosis. The pregnancy was interrupted at 14 weeks of gestation.

Because our study was a database retrospective study reporting on three cases found in our archive, informed patient consent was not required.

DISCUSSION

Multiple gestations with CHMCF create a serious dilemma for the management of precious, often long-awaited pregnancies. Until recently, given the serious complications attributed to CHMCF, the common practice was to advise termination of pregnancy [5,9,11].

In the last 20 years, however, several authors have reported uncomplicated pregnancies and the delivery of a viable fetus [8,10,13,17-20]. The general consensus remains that in all

cases, the patient should be informed of the potential risks of continuing such a pregnancy and the option of termination of pregnancy.

Elective abortion is chosen by 10–62% of the women with CHMCF. This wide variability can most likely be attributed to differences in religious and ethnic backgrounds as well as maternal age and marital status.

Of those who elect to continue their pregnancies, between 25%–50% ended with a spontaneous abortion or intrauterine fetal demise, usually ≤ 24 weeks of gestation. Estimating the complication rate is made more complex by differences in the definitions of complications in the literature. Some studies only refer to complications as life-threatening events, whereas others include each instance of vaginal bleeding during pregnancy. Given the high incidence of vaginal bleeding, especially in the first trimester, it is virtually impossible to establish a complication ratio. A more precise way of estimating the serious complication rate can be conducted by examining the percentage of induced abortions related to underlying medical complications. Unlike the 54% of maternal complications overall reported in the literature we reviewed, there was only an average of a 20% induced abortion rate for medical complications. Continuation of the pregnancy was not associated with a high risk of developing GTN [5,10,11]. Therefore, it might be prudent to suggest that conservative management of CHMCF pregnancies may be occasionally a reasonable option provided frequent follow-up is available.

Several risk factors are linked to a complete hydatidiform mole. A previous hydatidiform mole is considered the main risk factor, and increases the risk of a second hydatidiform conceptus by tenfold [21,22]. Another common risk factor is the extremes of maternal age, usually described as younger than 15 or older than 35 years of age. Women older than 35–40 years have a 2- to 7.5-fold risk for a molar conceptus, respectively [22].

One risk factor seldomly raised in the literature was fertility treatments [23]. Our overview indicated that 21% of the reported CHMCF pregnancies were attributed to assisted conception. This trend may not be coincidental and deserves additional investigation. Women at an advanced age are presumably more susceptible to abnormal fertilization [1]. Another assumption is that forced ovulation of more than one ovum by induction treatment increases the rate of a nuclear empty ovum [12]. Despite the worldwide trend of single embryo transfer in IVF cycles, controlled ovarian stimulation is still being conducted and the combination of both fertility treatment and the patient's advanced age may still be associated with the greater occurrence of CHMCF within the higher rate of twin pregnancies.

Recently, there has been a growing trend to perform non-invasive prenatal tests in twin pregnancies [24,25]. Therefore, it is crucial to conduct a scan prior to collect maternal blood sample to avoid conflicting results, including cases of CHMCF.

CONCLUSIONS

Records examined over a 10-year period in our medical center failed to reveal a significant association between assisted conception and the occurrence of CHMCF.

A review of the literature over the last 20 years shows that about one-quarter of the reported CHMCF pregnancies are attributed to assisted conception technology. However, these data are partially reported, making it impossible to draw firm conclusions. In view of the worldwide rise in assisted conception, the link between fertility treatment and CHMCF pregnancies should be further explored.

Correspondence

Dr. R. Maymon

Dept. of Obstetrics and Gynecology, Shamir Medical Center (Assaf Harofeh), Zerifin 70300, Israel

Phone: (972-8) 977-9695

Fax: (972-8) 977-9089

email: maymonrb@bezeqint.net

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Capsule

Microbial entrainment of metabolism

The metabolism of mammals is synchronized to daily cycles relating to sleep and mealtimes. It is not surprising that the gut microbiota, which aids in digestion, should also display daily cycling. **Kuang et al.** found that the gut microbiota can mediate daily cycles epigenetically. The microbiota induces rhythmic expression of histone deacetylase 3 (HDAC3) in epithelial cells of the small intestine, but not those of the colon. HDAC3 expression drives oscillations in intestinal metabolic gene expression, especially for nutrient transport and lipid metabolism. HDAC3 also directly activates estrogen-

related receptor α , which promotes lipid absorption. Consequently, mice that lack a gut microbiota lack daily regulation of their metabolism and become obese on high-fat chow. Disruption of HDAC3 cycling could be an explanation for human obesity associated with antibiotic damage to the microbiota and with sleep disruption caused by jet lag and nighttime working.

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Eitan Israeli

Capsule

Prioritizing Crohn’s disease genes by integrating association signals with gene expression implicates monocyte subsets

Genome-wide association studies have identified approximately 170 loci associated with Crohn’s disease (CD) and defining which genes drive these association signals is a major challenge. The primary aim of this study was to define which CD locus genes are most likely to be disease related. **Gettler and colleagues** developed a gene prioritization regression model (GPRM) by integrating complementary mRNA expression datasets, including bulk RNA-Seq from the terminal ileum of 302 newly diagnosed, untreated CD patients and controls, and in stimulated monocytes. Transcriptome-wide association and co-expression network analyses were performed on the ileal RNA-Seq datasets, identifying 40 genome-wide significant genes. Co-expression network analysis identified a single gene module, which was substantially enriched for CD locus

genes and most highly expressed in monocytes. By including expression-based and epigenetic information, the authors refined likely CD genes to 2.5 prioritized genes per locus from an average of 7.8 total genes. They validated their model structure using cross-validation and their prioritization results by protein-association network analyses, which demonstrated significantly higher CD gene interactions for prioritized compared with non-prioritized genes. Although individual datasets cannot convey all of the information relevant to a disease, combining data from multiple relevant expression-based datasets improves prediction of disease genes and helps further understanding of disease pathogenesis.

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Eitan Israeli

**“One does not ask of one who suffers: What is your country and what is your religion?
One merely says: You suffer, that is enough for me”**

Louis Pasteur (1822–1895), French biologist, microbiologist, and chemist renowned for his discoveries of the principles of vaccination, microbial fermentation and pasteurization