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Review article

A challenging case of twin pregnancy with complete hydatidiform mole and co-existing normal live fetus – A case report and review of the literature

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ABSTRACT

Hydatidiform mole coexisting with a normal live fetus in a twin pregnancy is extremely rare. Management of these cases is challenging due to the risk of severe antepartum and post-partum complications. Herein, we report the case of a 24-year-old gravida 2 para 1 who presented at 28 weeks gestation with severe preeclampsia, vulvar edema and a serum β-HCG of 285,000 IU/mL. Ultrasonography demonstrated a single live intra-uterine pregnancy with concurrent hydatidiform mole. Conservative management with magnesium sulfate and anti-hypertensive medications was initiated however the patient developed HELLP syndrome and required urgent delivery at 33 weeks. Copious molar tissue was removed from the uterus during delivery. Four weeks post-partum, her β-HCG had dropped to 14,000 IU/ml and continued to decline at 6 weeks (2900 IU/ml). However, at eight weeks, it increased to 3500 IU/ml and the patient was treated with nine cycles of intramuscular methotrexate. Current guidelines for management of a twin pregnancy with coexistent mole recommend close clinical monitoring if the mother and fetus are stable and urgent delivery in the setting of complications. During the post-partum period, careful follow up with clinical evaluation and serial serum β-HCG is important for the diagnosis and treatment of persistent trophoblastic disease.

1. Introduction

Complete hydatidiform mole coexisting with a viable live fetus (CMCF) is an extremely rare phenomenon, occurring in approximately 1/22,000–1/100,000 pregnancies worldwide (Sebire et al., 2002; Vaisbuch et al., 2005). Asian countries have the highest reported incidence (Bracken, 1987) which has been attributed to differences in nutritional and socio-economic factors, such as a high frequency of vitamin A deficiency (Berkowitz and Goldstein, 1996). Management of these cases is challenging due to the increased risk of both antenatal and perinatal complications including ante-partum hemorrhage and intra-uterine fetal demise (Massardier et al., 2009; Sebire et al., 2002; Suksai et al., 2017). Less than 50% of these cases will result in a live birth and a significant proportion require early termination due to the development of severe pre-eclampsia(Suksai et al., 2017). Furthermore, up to 63% of patients with CMCF will develop persistent disease after delivery, half of whom will have metastatic disease (M Steller et al., 1994). Thus, at the time of diagnosis, a careful evaluation of the ongoing maternal and fetal risks is crucial to proper patient counselling regarding pregnancy continuation.

2. Case report

Herein we report the case of a 24-year-old gravida 2 para 1 who presented at 28 weeks gestation to the emergency labor ward at Dhaka Medical College Hospital with severe pre-eclampsia and vulvar edema. Her obstetrical history was notable for an uncomplicated spontaneous vaginal delivery four years earlier. She was anemic (Hb 9.0 gm/dl) and hypertensive with a blood pressure at presentation of 160/100 mmHg. An ultrasound demonstrated a single live intra-uterine pregnancy which was determined to be 28 weeks gestation based on dates and estimated fetal weight (Figs. 1 and 2). In addition, a large hydatidiform mole was noted and subsequent β-HCG measurement was elevated at 285,000 IU/ml. The patient was extensively counseled about maternal and fetal risks of continuing the pregnancy, most notably the risk of developing eclampsia. However, despite this she declined immediate delivery and elected for conservative management with anti-hypertensive medications and magnesium sulfate. An ultrasound was performed which did not demonstrate any fetal anomalies. After obtaining blood pressure control, she was discharged home with close follow-up. At 33 weeks gestation she was re-admitted due to concern

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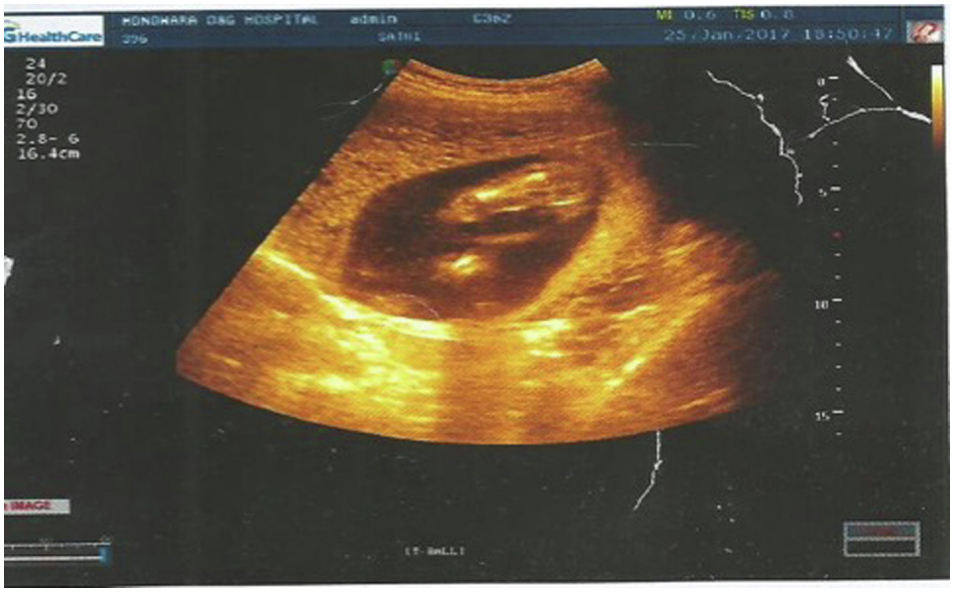

Fig. 1. Ultrasound findings at 16 weeks gestation demonstrating normal fetal parts alongside molar tissue.

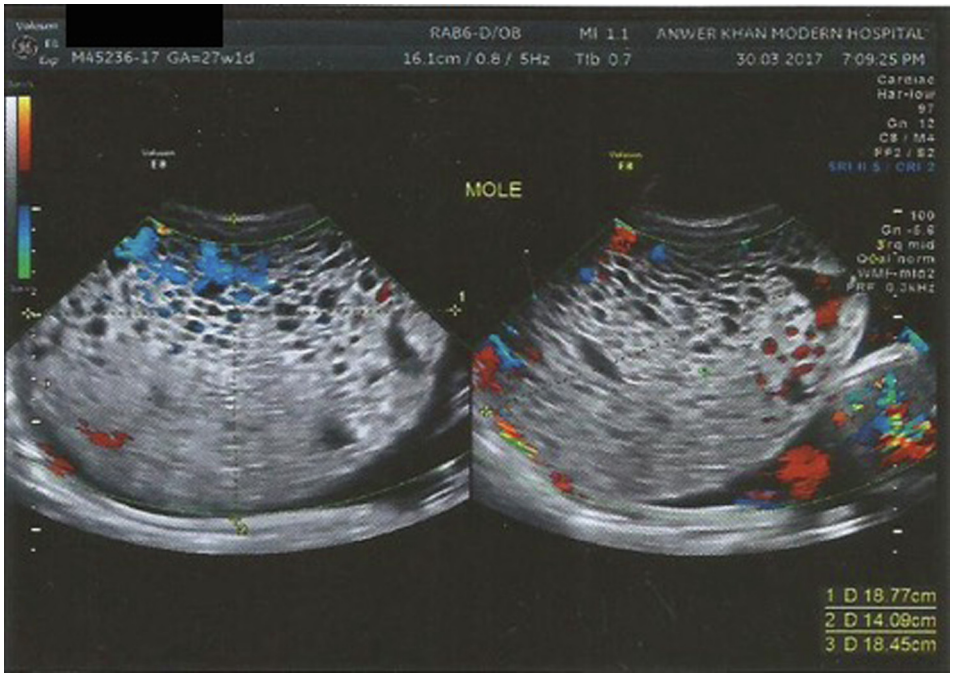

Fig. 2. Ultrasound findings at 32 weeks gestation demonstrating characteristic vesicular "snowstorm" pattern of molar tissue.

for the development of HELLP syndrome with impending eclampsia. At this time, she was noted to have frank hematuria and ascites. Her hemoglobin was 8.2gml/dl with evidence of hemolysis and her coagulation factors were prolonged. She was resuscitated and transfused, and the decision was made to proceed with urgent delivery. A live male infant weighing 1.8 kg was delivered by caesarean section. During the delivery of the placenta, a large volume of molar tissue was removed from the uterus (Fig. 3) and two additional units of blood were transfused due to intra-operative bleeding. The placenta and molar tissue were sent for histopathology which confirmed the finding of both a complete hydatidiform mole and a normal placenta. Post-partum, the infant was admitted to the neonatal ICU and discharged in stable condition after two weeks. The patient was monitored closely with serial β-HCG measurements. Four weeks after delivery, the β-HCG had spontaneously dropped to 14,000 IU/ml and at six weeks it had decreased further to 2900 IU/ml. However, at eight weeks it had increased to 3500 IU/ml on two consecutive readings. Given the abnormal β-HCG regression pattern, the decision was made to treat for a persistent mole. Based on a WHO score of 5 after staging, she was administered intramuscular methotrexate for nine cycles which resulted in normalization of her β-HCG levels to less than 6 IU/ml. Consent was obtained from the patient prior to publication of this Case report. Institutional review board approval was not required.

3. Review of the literature

Gestational trophoblastic disease (GTD) includes a spectrum of inter-related tumors including complete and partial hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT) that have varying

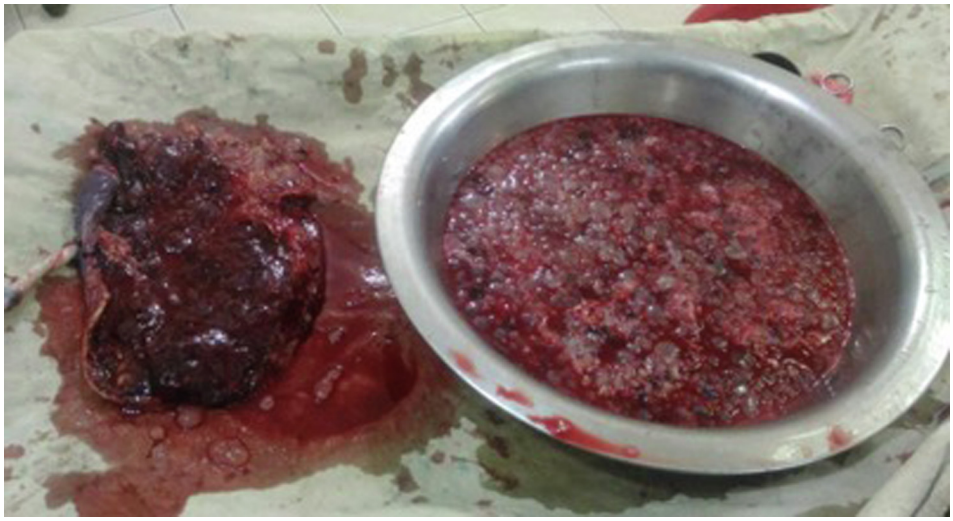

Fig. 3. Post-operative findings – Normal placenta (left) and molar tissue (right).

propensities for local invasion and metastases (Bagshawe, 1976; Berkowitz and Goldstein, 2013; Ngan et al., 2018). Persistent GTD, also called gestational trophoblastic neoplasia (GTN) is among the rare human malignancies that can be cured in the presence of widespread metastases (Bagshawe, 1976; Berkowitz and Goldstein, 2013; Ngan et al., 2018). Complete hydatidiform moles with a coexisting fetus (CMCF) is one of the rarest presentations of trophoblastic disease, with just over two hundred cases reported in the literature in the past two decades (Vimercati et al., 2013). Twin pregnancy with a partial mole and a viable fetus or a singleton pregnancy with a partial molar placenta are even less common (Atuk et al., 2018)

CMCF can be classified into three major types (Matsui et al., 2000; Piura et al., 2008). The first, which was reported here, is a twin gestation in which one twin is diploid with a normal placenta (46 chromosomes, 23 maternal and 23 paternal) and the other twin is a complete hydatidiform mole (46 chromosomes of paternal origin). The second is a singleton triploid fetus with partial hydatidiform mole placenta (69 chromosomes, 23 maternal and 46 paternal) and the third is a twin gestation in which one fetus is diploid with normal placenta (46 chromosomes, 23 maternal and 23 paternal) and the other is triploid with partial hydatidiform mole placenta (69 chromosomes, 23 maternal and 46 paternal) (Matsui et al., 2000; Piura et al., 2008). In complete hydatidiform moles there is a lack of identifiable embryonic or fetal tissues and the chorionic villi exhibit generalized hydatidiform swelling and diffuse trophoblastic hyperplasia (Heller, 2018). Cytogenic studies have demonstrated that complete moles most commonly display a 46xx karyotype and molar chromosomes are entirely of paternal origin (Hoffner and Surti, 2012). Historically, it was thought that complete moles arise from an anucleate ovum which has been fertilized by a haploid sperm that duplicates its own chromosomes (Yamashita et al., 1979). However, more recent evidence argues against the presence of anucleate eggs, and suggests that complete moles may develop instead from the post-zygotic diploidization of a triploid conception (Golubovsky, 2003; Hoffner and Surti, 2012). Partial moles have a triploid karyotype (69 chromosomes), with an extra haploid set of chromosomes derived from father (Lawler et al., 1991).

Twin pregnancy with complete hydatidiform mole has a higher risk of maternal complications as compared to a singleton pregnancy or a non-molar twin pregnancy (Sebire et al., 2002; Suksai et al., 2017). These include obstetrical complications such as antepartum hemorrhage, severe early-onset pre-eclampsia or eclampsia, placenta previa, preterm premature rupture of the membranes and preterm labor (Kihara et al., 2012; Lin et al., 2017; Rohilla et al., 2015) as well as fetal complications including spontaneous abortion, intra-uterine growth restriction and intra-uterine fetal demise (Lin et al., 2017; Rohilla et al., 2015; Wee and Jauniaux, 2005). Furthermore, maternal medical complications associated with molar pregnancy such as thyrotoxicosis, theca lutein cysts and persistent trophoblastic disease are also seen (Massardier et al., 2009; Sebire et al., 2002; Massardier et al., 2009; M Steller et al., 1994).

Management of these cases is complex, as the fair possibility of fetal survival is weighed against the expected risk of maternal complications. In a large review of 72 cases by Lin et al, up to 67% of patients experienced a significant antepartum hemorrhage and 30% of patients developed early onset pre-eclampsia (Lin et al., 2017). Furthermore, there was a 15% rate of respiratory distress at presentation and a 1.4% maternal death rate in this series (Lin et al., 2017). Suksai et al confirmed these findings in a review of cases of CMCF from 1993 to 2016, demonstrating the significant maternal risk involved in continuation of these pregnancies (Suksai et al., 2017).

Given these risks, a significant number of CMCF pregnancies end in termination either electively or due to maternal complications (Ozarpaci et al., 2005; Sheik et al., 2015; Soysal et al., 1996). In a review of 14 cases by Massardier et al, 57% of pregnancies ended in termination of which 21% were electively terminated and 79% were terminated due to maternal or fetal complications (Massardier et al., 2009). Sebire et al reported a 33% rate of elective termination and a 43% fetal loss rate prior to 24 weeks in women who elected to continue their pregnancy (Sebire et al., 2002). In a review of 206 cases, Suksai et al reported a lower elective termination rate of only 11.7% but a subsequent termination rate of 32% due to maternal complications with an additional 18% of pregnancies ending in fetal loss(Suksai et al., 2017). Given these findings, it is unsurprising that the live birth rate reported in the literature is low but variable ranging from 21% (Massardier et al., 2009) to 45% in a series of 13 CMCF cases from Italy (Giorgione et al., 2017). Lin et al reported at 52% live birth rate in their study however less than one third of these women delivered at term (Lin et al., 2017).

Despite these findings, a number of authors have reported good outcomes with conservative management, and thus after counselling the option remains to continue the pregnancy under close observation (Anderson et al., 1996; Bruchim et al., 2000; Peng et al., 2014; Piura et al., 2008; Winter et al., 1999). Predictors of good pregnancy outcomes include lower β-HCG levels at diagnosis, a later gestational age at diagnosis and a lack of antenatal maternal medical complications which together suggest that favorable outcomes are associated with less pronounced molar growth (Bristow et al., 2019; Suksai et al., 2017).

Post-partum, the risk of development of persistent gestational

trophoblastic disease, also known as gestational trophoblastic neoplasia (GTN), is significant. Steller et al compared 8 patients with CMCF to 71 patients with singleton molar pregnancies in a 1994 review. They noted a significantly increased risk of GTN in the CMCF pregnancies as compared to the singleton moles (63% vs 14%) and a high rate of metastatic disease (38%) (M Steller et al., 1994). However, in a separate review of 8 cases CMCF and 154 singleton molar pregnancies, Neimann et al found a similar rate of GTN between the groups (25% vs 17% respectively) (Niemann et al., 2007). Massardier et al reported a 50% risk of GTN in their cohort of 14 patients, all of whom had low risk WHO scores at diagnosis(Massardier et al., 2009) whereas 27% of patients with GTN required multi-agent chemotherapy in a review by Bruchim et al (Bruchim et al., 2000). Many case reports have also reported requiring aggressive multi-agent chemotherapy to achieve a cure (Braga et al., 2017; Peng et al., 2014; M.A. Steller et al., 1994) however the majority of patients appear to be adequately treated with single agent methotrexate (Fishman et al., 1998). In a larger retrospective study of 77 patients, Sebire et al demonstrated a much lower rate of post-partum GTN (19%). In this series, 75% of patients were cured with single-agent chemotherapy where as 26% required multi-agent treatment. Importantly, they reported that the risk of GTN was similar whether women elected to terminate their pregnancy in the first trimester or to continue their pregnancy (Sebire et al., 2002). This finding was confirmed by Giorgione et al who also found no decrease In GTN rates associated with early elective termination (Giorgione et al., 2017). However, the development of adverse pregnancy outcomes in women who continue their pregnancies has been linked to a significantly higher rate of GTN (Lin et al., 2017; Matsui et al., 2000; Suksai et al., 2017) as has higher β-HCG at presentation, lower gestational age at delivery, and lower fetal viability rates (Lin et al., 2017).

4. Conclusion

The general trend in managing pregnancy in twins with coexistent mole is to terminate in anticipation of complications. However, with close maternal and fetal monitoring and individualized care, optimal outcomes can be achieved (Rohilla et al., 2015). The decision to continue the pregnancy will largely depend on the presence or absence of complications to the mother or baby, prior obstetric history, as well as the woman's wishes. During postpartum period careful follow up is important for the diagnosis and treatment of persistent trophoblastic disease.

Author contributions

The contribution of the individual authors is as follows: Dr. Lufta Begum Lipi collected the case data and was involved in writing the manuscript. Dr. Lauren Philp was involved in writing and editing the manuscript and Dr. Annekathryn Goodman was the Senior Responsible Author who supervised data collection and performed manuscript editing. There are no funding sources to report.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

References

Anderson, C., Deiter, R., Motz, M., Goldstein, J., 1996. Complete hydatidiform mole with a coexistant healthy, viable fetus near term; a case report. J. Reprod. Med. 41, 55–58.

Atuk, F.A., Binti, J., Basuni, M., 2018. Molar pregnancy with normal viable fetus presenting with severe pre-eclampsia: a case report. J. Med. Case Rep. 12, 12–14.

Bagshawe, D., 1976. Risk and prognostic factors in trophoblastic disease. Cancer 38, 1373–1385.

Berkowitz, R., Goldstein, D., 2013. Current advances in the management of gestational trophoblastic disease. Gynecol. Oncol. 128, 3–5. https://doi.org/10.1016/j.ygyno.2012.07.116.

Berkowitz, R., Goldstein, D., 1996. Epidemiology and risk factors. NEJM 335, 1740–1748.

Bracken, M.B., 1987. Incidence and aetiology of hydatidiform mole: an epidemiological review. Br. J. Obstet. Gynaecol. 94, 1123–1135.

Braga, A., Obeica, B., Werner, H., Sun, S.Y., Júnior, J.A., Filho, J.R., Júnior, E.A., 2017. A twin pregnancy with a hydatidiform mole and a coexisting live fetus: prenatal diagnosis, treatment, and follow-up. J. Ultrason. 17, 299–305. https://doi.org/10.15557/JoU.2017.0044.

Bristow, R., Shumway, J., Khouzami, A., Witter, F., 2019. Complete hydatidiform mole and surviving coexistent twin. Obstet. Gynecol. Surv. 51, 705–709.

Bruchim, I., Kidron, D., Amiel, A., Ph, D., Altaras, M., Fejgin, M.D., 2000. Complete hydatidiform mole and a coexistent viable fetus: report of two cases and review of the literature. Gynecol. Oncol. 77, 197–202. https://doi.org/10.1006/gyno.2000.5733.

Fishman, D., Padilla, L., Pacita, K., Cohen, L., Frederiksen, M., Lurain, J., 1998. Managemetn of Twin Pregnancies consisting of a complete hydatidiform mole and normal fetus. Obstet. Gynecol. 91, 546–550.

Giorgione, V., Cavoretto, P., Cormio, G., Valsecchi, L., Vimercati, A., De Gennaro, A., Rabaiotti, E., Candiani, M., Mangili, G., 2017. Prenatal diagnosis of twin pregnancies with complete hydatidiform mole and coexistent normal fetus: a series of 13 cases. Gynecol. Obstet. Invest. 82, 404–409. https://doi.org/10.1159/000448139.

Golubovsky, M.D., 2003. Postzygotic diploidization of triploids as a source of unusual cases of mosaicism, chimerism and twinning. Hum. Reprod. 18, 236–242. https://doi.org/10.1093/humrep/deg060.

Heller, D.S., 2018. Update on the pathology of gestational trophoblastic disease. APMIS 126, 647–654. https://doi.org/10.1111/apm.12786.

Hoffner, L., Surti, U., 2012. The genetics of gestational trophoblastic disease: a rare complication of pregnancy. Cancer Genet. 205, 63–77. https://doi.org/10.1016/j.cancergen.2012.01.004.

Kihara, M., Usui, H., Tanaka, H., Inoue, H., Matsui, H., Shozu, M., 2012. Complicating pre-eclampsia as a predictor of poor survival of the fetus in complete hydatidiform mole coexistant with twin fetus. J. Reprod. Med. 57, 325–328.

Lawler, D., Fisher, R., Dent, J., 1991. A prospective genetic study of complete and partial hydatidiform moles. Am. J. Obstet. Gynecol. 164, 1270–1277.

Lin, L.H., Maestá, I., Braga, A., Sun, S.Y., Fushida, K., Francisco, R.P.V., Elias, K.M., Horowitz, N., Goldstein, D.P., Berkowitz, R.S., 2017. Multiple pregnancies with complete mole and coexisting normal fetus in North and South America: a retrospective multicenter cohort and literature review. Gynecol. Oncol. 145, 88–95. https://doi.org/10.1016/j.ygyno.2017.01.021.

Massardier, J., Golifer, F., Journet, D., Frappart, L., Zalaquett, M., Schott, A., Lenoir, V., Dupuis, O., Hajri, T., Raudrant, D., 2009. Twin pregnancy with complete hydatidiform mole and coexistent fetus Obstetrical and oncological outcomes in a series of 14 cases. Eur. J. Obstet. Gynecol. Reprod. Biol. 143, 84–87. https://doi.org/10.1016/j.ejogrb.2008.12.006.

Matsui, H., Sekiya, S., Hando, T., Wake, N., Tomoda, Y., 2000. Hydatidiform mole coexistent with a twin live fetus: a national collaborative study in Japan. Hum. Reprod. 15, 608–611.

Ngan, H.Y.S., Seckl, M.J., Berkowitz, R.S., Xiang, Y., Golfier, F., Sekharan, P.K., Lurain, J.R., Massuger, L., 2018. Update on the diagnosis and management of gestational trophoblastic disease. Gynecol. Obstet. 143, 79–85. https://doi.org/10.1002/ijgo.12615.

Niemann, I., Sunde, L., Petersen, L.K., 2007. Evaluation of the risk of persistent trophoblastic disease after twin pregnancy with diploid hydatidiform mole and coexisting normal fetus. Am. J. Obstet. Gynecol. 42, 1–5. https://doi.org/10.1016/j.ajog.2007.02.038.

Ozarpaci, C., Yalti, S., Gurbuz, B., Ceylan, S., Cakar, Y., 2005. Complete hydatidiform mole with coexistent live fetus in dichorionic twin gestation. Arch Gynecol Obs. 271, 270–273. https://doi.org/10.1007/s00404-004-0642-x.

Peng, H., Huang, K., Chueh, H., Adlan, A., Chang, S., Chyi-long, L., 2014. Term delivery of a complete hydatidiform mole with a coexisting living fetus followed by successful treatment of maternal metastatic gestational trophoblastic disease. Taiwan. J. Obstet. Gynecol. 53, 397–400. https://doi.org/10.1016/j.tjog.2013.02.005.

Piura, B., Rabinovich, A., Hershkovitz, R., Maor, E., Mazor, M., 2008. Twin pregnancy with a complete hydatidiform mole and surviving co-existent fetus. Arch. Gynecol. Obs. 278, 377–382. https://doi.org/10.1007/s00404-008-0591-x.

Rohilla, M., Singh, P., Kaur, J., Jain, V., Gupta, N., 2015. Individualistic approach to the management of complete hydatidiform mole with coexisting live fetus. Eur. J. Obstet. Gynecol. 191, 39–42. https://doi.org/10.1016/j.ejogrb.2015.05.017.

Sebire, N.J., Foskett, M., Paradinas, F.J., Fisher, R.A., Francis, R.J., Short, D., Newlands, E.S., Seckl, M.J., 2002. Outcome of twin pregnancies with complete hydatidiform mole and healthy co-twin. Lancet 359, 2165–2166.

Sheik, S., Al-riyami, N., Mathew, N.R., Al-sukaiti, R., Qureshi, A., Mathew, M., 2015. Twin pregnancy with a complete hydatidiform mole and a coexisting live fetus. Sultan Qaboos Univ. Med. J. 15, 550–553. https://doi.org/10.18295/squmj.2015.15.04.019.

Soysal, M., Kara, S., Ekici, E., 1996. Twin pregnancy with a fetus and a complete hydatidiform mole. Arch. Gynecol. Obstet. 259, 41–44.

Steller, M., Genest, D., Bernstein, M., Lage, J., Goldstein, D., Berkowitz, M., 1994a. Natural history of twin pregnancy with complete hydatidiform mole and coexisting fetus. Obstet. Gynecol. 83, 35–42.

Steller, M.A., Genest, D., Bernstein, M., Lage, J., Goldstein, D., Berkowitz, R., 1994b. Clinical features of multiple conception with partial or complete molar pregnancy and coexisting fetuses. J. Reprod. Med. 39, 147–154.

Suksai, M., Suwanrath, C., Kor-anantakul, O., Geater, A., Hanprasertpong, T., Atjimakul, T., Pichatechaiyoot, A., 2017. Complete hydatidiform mole with co-existing fetus: predictors of live birth. Eur. J. Obstet. Gynecol. 212, 1–8. https://doi.org/10.1016/j.ejogrb.2017.03.013.

Vaisbuch, E., Ben-arie, A., Dgani, R., Perlman, S., 2005. Twin pregnancy consisting of a complete hydatidiform mole and co-existent fetus: report of two cases and review of

literature. Gynecol. Oncol. 98, 19–23. https://doi.org/10.1016/j.ygyno.2005.02.002.
Vimercati, A., Gennaro, A.C. De, Grasso, Silvana, Cobuzzi, I., Grasso, S., Abruzzese, M., Fascilla, F., Cormio, G., Selvaggi, L., 2013. Two cases of complete hydatidiform mole and coexistent live fetus. J. Prenat. Med. 7, 1–4.
Wee, L., Jauniaux, E., 2005. Prenatal diagnosis and management of twin pregnancies complicated by a co-existing molar pregnancy. Prenat. Diagn. 25, 772–776. https://doi.org/10.1002/pd.1272.
Winter, C., Brock, B.V., Fligner, C., Brown, Z.A., 1999. Coexistent surviving neonate twin and complete Hydatidiform mole. Am. J. Roentgenol. 172, 451–453.
Yamashita, K., Wake, N., Araki, T., Ichinoe, K., Makoto, K., 1979. Human lymphocyte antigen expression in hydatidiform mole: androgenesis following fertilization by a haploid sperm. Am. J. Obstet. Gynecol. 135, 597–600.