Received: 9 July 2019 | Revised: 15 December 2019 | Accepted: 12 January 2020

DOI: 10.1002/ccr3.2703

CASE REPORT

Clinical Case Reports Open Access WILEY

Molar and nonmolar triploidy: Recurrence or bad luck

Brianne Robinson[1] | **Jo-Ann Brock**[2] | **Craig Midgen**[3] | **Jillian Coolen**[4]

[1]Dalhousie Medical School, Halifax, NS, Canada

[2]Departments of Anatomic Pathology and Obstetrics and Gynaecology, Dalhousie University, Halifax, NS, Canada

[3]Department of Anatomic Pathology, Dalhousie University, Halifax, NS, Canada

[4]Department of Obstetrics and Gynaecology, Dalhousie University, Halifax, NS, Canada

Correspondence
Brianne Robinson, Dalhousie Medical School, 5849 University Avenue, Halifax, NS B3H 4R2, Canada.
Email: brianne.robinson@dal.ca

Abstract

In triploid pregnancies, the parental origin of the extra genome determines the phenotype and placental and fetal outcomes. Molecular genetics and placental pathology enable differentiation of molar vs nonmolar pregnancy to guide future planning.

KEYWORDS

genomic imprinting, hydatidiform mole, triploidy

1 | INTRODUCTION

Molar and triploid pregnancies result from abnormal contributions of maternal or paternal genomic contributions to the conceptus. Diploid pregnancies with only paternally derived genomes present as complete molar pregnancies, with no development of embryonic tissue. In triploid pregnancies, the parental origin of the extra genome determines the phenotype and outcomes of the fetus and placenta, with differential expression of maternal and paternal genes influencing normal embryonic development.[1] When the third haploid genome is paternally derived, the typical presentation is a partial molar pregnancy; whereas when the third haploid genome is maternally derived, the presentation is a nonmolar triploid pregnancy.[1] While fetal development is common in both types of triploid pregnancy, establishing a diagnosis of partial molar vs nonmolar pregnancy is important for subsequent patient management. We report the clinical, ultrasound, molecular, and histopathologic findings of a patient who in two sequential pregnancies had a partial molar pregnancy (presumed diandric triploidy), followed by a digynic triploidy.

2 | CASE

A 35-year-old gravida 3, para 0, abortus 2 was referred to maternal-fetal medicine for management of her third pregnancy. Neither the patient nor her partner had any significant past medical or family history, with the exception that their previous two pregnancies together had resulted in early pregnancy losses. The first pregnancy was a spontaneous abortion at 7 weeks gestation managed expectantly without complication. The second was a missed abortion at eight weeks gestation managed with manual vacuum aspiration (molecular genetics unavailable). Subsequent pathologic assessment diagnosed this loss as a partial mole based on the findings of focal trophoblastic hyperplasia and hydropic villi (Figure 1A). Given this diagnosis, appropriate serial beta-hCG follow-up was completed with no evidence of gestational trophoblastic neoplasia. As often the case, she did not have any ultrasound findings or clinical symptoms or signs suggestive of molar pregnancy, which makes preoperative diagnosis challenging.[2-4]

At the time of an early ultrasound in her third pregnancy, although she was certain of the date of her last menstrual period and had been having regular menstrual cycles, fetal size

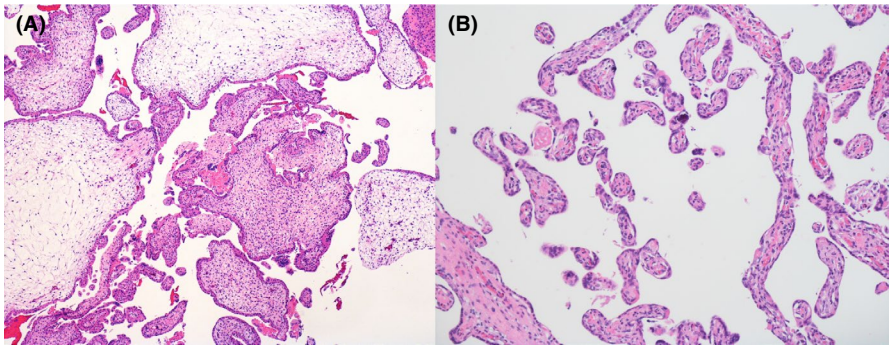

FIGURE 1 Placental pathology from the patient's A, partial molar pregnancy demonstrating a mixture of hydropic villi with mild trophoblast hyperplasia and small nonhydropic villi and B, nonmolar triploidy pregnancy demonstrating accelerated villous maturation consistent with placental insufficiency and no features of partial mole

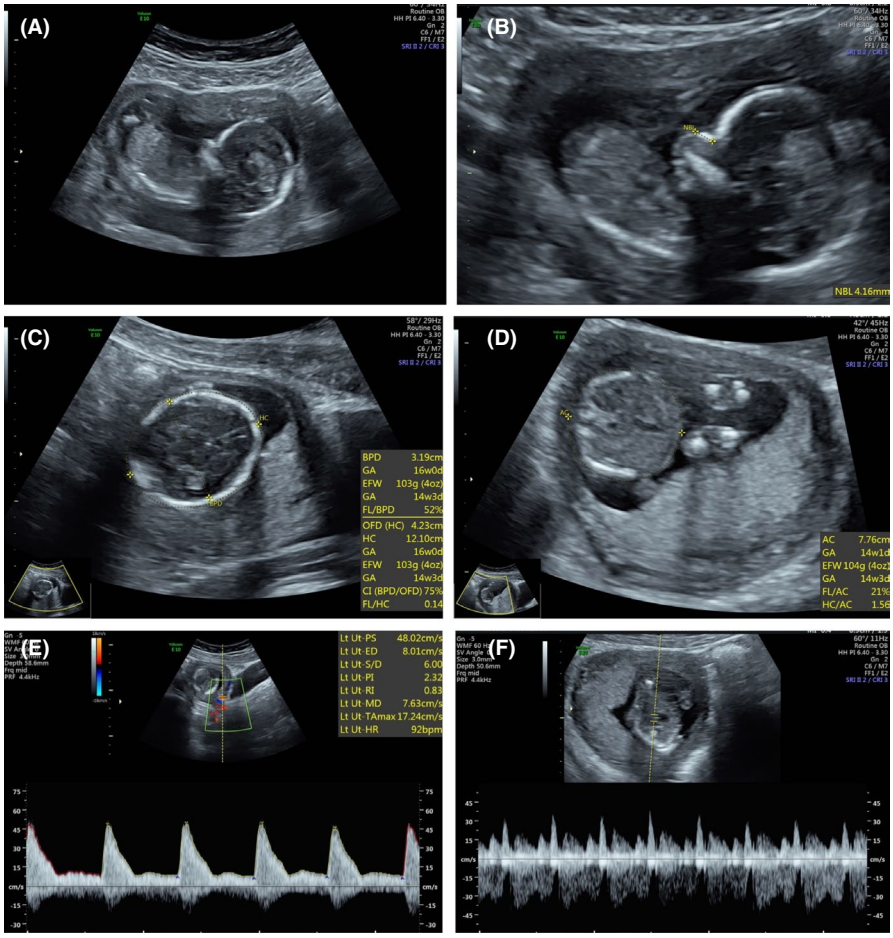

FIGURE 2 Prenatal 2D sonographic views of the fetus at 16 weeks gestational age. A, Mid-sagittal view of the fetus demonstrating oligohydramnios. B, Facial profile with retrognathia; an anomaly commonly associated with triploidy. C, Cranial measurements appropriate for gestational age. D, Small abdominal circumference in keeping with asymmetric fetal growth restriction. E, Increased maternal uterine artery pulsatility index and notching. F, Abnormal ductus venosus waveform with deep a-wave

was smaller than expected. Her estimated date of delivery was adjusted, and she was scheduled for a follow-up ultrasound in 2 weeks' time for nuchal translucency (NT) measurement. At that ultrasound, there had been interval fetal growth and early fetal anatomic review was within normal limits, including the NT measurement. Both the PAPP-A and free beta-hCG measurements from her early maternal serum biochemistry were noted to have low multiples of the median, 0.05 MoM and 0.14 MoM, respectively; however, her combined first trimester screening result for Down syndrome was below the screening threshold; therefore, she declined genetic diagnostic testing.

Throughout the first and into the second trimester, the patient experienced chronic vaginal bleeding without an obvious cause identified. Because of persistent bleeding, an ultrasound was done at 16 weeks and was concerning for early-onset asymmetric fetal growth restriction (estimated fetal weight less than the 2nd percentile), uteroplacental insufficiency as demonstrated by an increased mean maternal uterine artery pulsatility index and oligohydramnios (Figure 2). No obvious structural anomalies were identified at that time; however, imaging was limited due to small fetal size and oligohydramnios. Investigations included clinical assessment for ruptured membranes, with no evidence of fern, and maternal serology to screen for perinatal infection, which was negative. Amniocentesis for a potential genetic etiology associated with early growth restriction was declined. After being

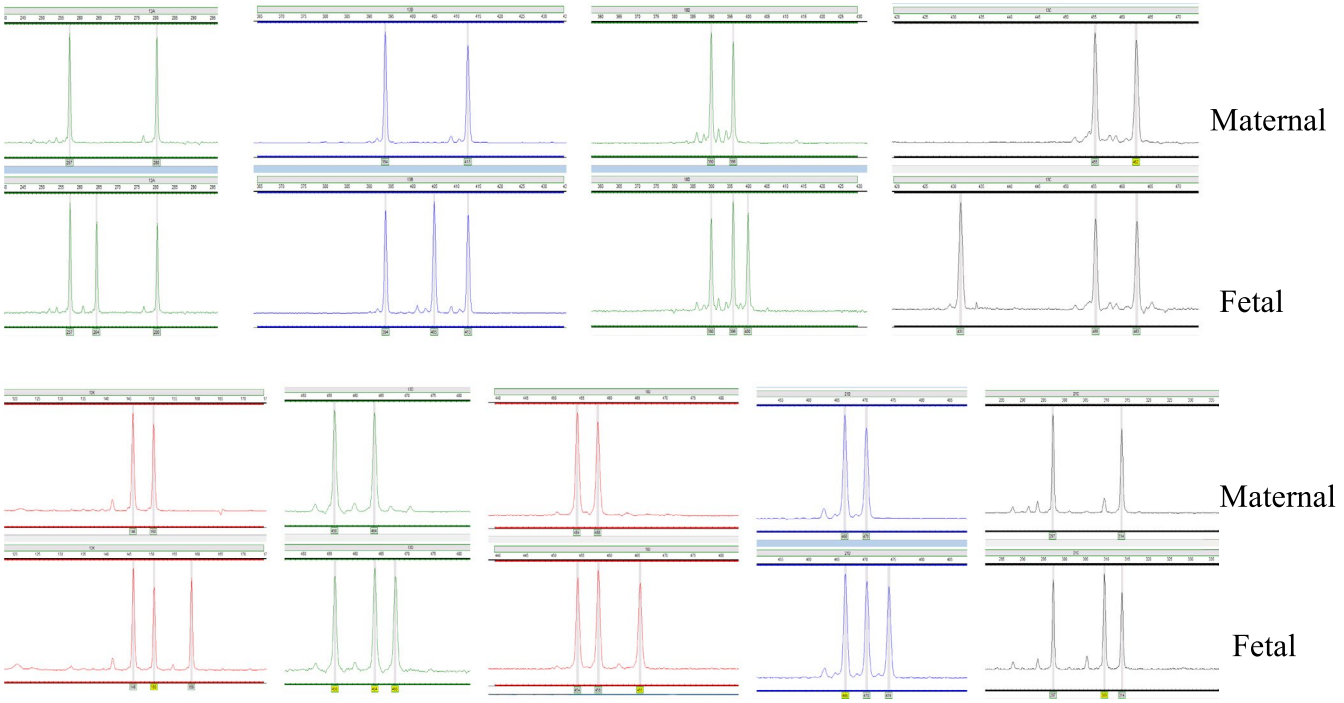

FIGURE 3 QF-PCR of STR markers suggesting maternal inheritance of the third allele in fetal triploidy

counselled regarding the potential outcomes and options, the patient chose to continue with expectant management, and aspirin was initiated.

One week later, an intrauterine fetal demise was diagnosed. The patient proceeded with an uncomplicated dilatation and evacuation under ultrasound guidance. Rapid aneuploidy detection performed from DNA of the fetal tissue was consistent with triploidy in a fetus with two X chromosomes and one Y chromosome. Quantitative fluorescent amplification of multiple short tandem repeat (STR) markers on chromosomes 13, 18, 21, X and Y, was done using the Devyser Compact kit (Figure 3). Nine of 16 autosomal makers demonstrated three distinct alleles in the fetus in a 1:1:1 ratio, all of which were consistent with fetal inheritance of two maternal alleles. Four markers showed only two allele peak sizes in the fetus in a 2:1 ratio (consistent with triploidy), and three markers were uninformative with only one allele peak size in the fetus (data not shown). None of these markers were inconsistent with fetal inheritance of two maternal alleles (data not shown). Polymorphic markers on the X and Y chromosomes and presence of the SRY gene were consistent with two maternally inherited X chromosomes and one Y chromosome (data not shown). The most likely parental origin of the extra chromosomes was determined to be maternal, in keeping with digynic triploidy. Placental pathology showed accelerated villous maturation consistent with placental insufficiency (Figure 1B). Given the previous history of a partial molar pregnancy, additional sections of placental tissue were reviewed by two pathologists and no histopathologic features of partial mole were seen. The final diagnosis was determined to be digynic nonmolar triploidy.

3 | DISCUSSION

Conceptuses with abnormal complements of maternal and paternal genotypes often present with characteristic clinical findings. The abnormal pregnancy development is a consequence of the abnormal relative contribution of maternal and paternal genomic content, related to different patterns of gene expression found in the maternally and paternally derived genomes.[1] Molar pregnancies are classified as partial or complete hydatidiform moles and can be distinguished based on characteristic cytogenetic and morphologic features.

The genomic imprint is established differently in the gametes of males and females, and the conceptus requires both a maternal and paternal haploid genome contribution for normal development to occur. A diploid conceptus containing 46 chromosomes that are all paternal origin (diandric diploidy) presents as a complete hydatidiform mole, with an incidence of 1 in 1500 pregnancies.[1,5] Two possible mechanisms result in diandric diploidy. In the most common mechanism, an enucleated ovum is fertilized by one sperm followed by duplication of the haploid genome.[1] Less commonly, an enucleated ovum is fertilized by two sperm both contributing haploid chromosome complements.[1]

A triploid conceptus contains three copies of each chromosome resulting in a total of 69 chromosomes. Triploidy is

a common chromosomal anomaly associated with 8%-10% of spontaneous abortions.[1] In triploid pregnancies, the extra haploid set of chromosomes can be either maternally or paternally derived. Maternally derived digynic triploidy typically results from an error in meiosis II, and fertilization of a diploid ovum by a normal haploid sperm.[6] Paternally derived diandric triploidy commonly results from the fertilization of a normal haploid ovum by a single diploid or two haploid spermatozoa and accounts for close to 90% of partial molar pregnancies.[6]

Complete and partial molar pregnancies can be distinguished based on a constellation of clinical, ultrasound, and histopathologic features. Clinically, patients with complete molar pregnancies present with irregular vaginal bleeding, hyperemesis, uterine enlargement and an abnormally high quantitative beta-hCG. Complete moles are associated with the development of diffuse trophoblastic hyperplasia with abnormal cystic villi and the absence of embryonic tissue.[1,7] In contrast, partial moles are characterized by focal trophoblastic proliferation and cystic villi with the presence of embryonic tissue.[5] These findings suggest maternal chromosomes are required for the development of the embryoblast.[6] Diandric triploid pregnancies typically demonstrate normal fetal growth with a proportionately grown or a microcephalic head, and placental changes characteristic of a partial mole. Digynic triploid pregnancies usually have asymmetric fetal growth restriction, and a small placenta lacking characteristic molar changes. Digynic triploidy is therefore often referred to as nonmolar triploidy. Fetal anomalies are common in triploid fetuses, and features such as syndactyly do not appear to differ between diandric and digynic groups.[7]

For this patient, a combination of molecular genetic testing to establish the likely parent of origin of the extra haploid genome in a triploid pregnancy, and histopathology to assess for molar elements in the placenta, provided a diagnosis of a nonmolar digynic triploidy. This was a case of bad luck rather than recurrence; therefore, she did not require completion of serial beta-hCG monitoring and did not need to avoid pregnancy. In addition, we could reassure her that her risk of a recurrent molar pregnancy was low, 0.6%-2% after one molar pregnancy, compared to 15% after 2 consecutive molar pregnancies due to mutations such as NLRP7 and KHDC3L.[8-10] In her subsequent pregnancy, the patient's luck finally changed as she went on to have a normal pregnancy and liveborn.

4 | CONCLUSION

This case highlights the combined roles of molecular genetics and placental histopathology for establishing an abnormal pregnancy diagnosis and appropriate management plan for the patient. Establishing a diagnosis of complete or partial molar pregnancy is important for maternal medical management. Given the risk for developing gestational trophoblastic neoplasia, follow-up includes serial beta-hCG monitoring, and effective contraception is recommended to avoid pregnancy for up to 6 months after the beta-hCG has normalized.[8] In contrast, a nonmolar triploid pregnancy is not at risk for developing gestational trophoblastic neoplasia.

ACKNOWLEDGMENTS

The authors would like to acknowledge the patient for providing consent to share her case.

CONFLICT OF INTEREST

The authors of this study have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

JAB: Maternal Fetal Medicine Specialist and Clinical Molecular Geneticist contributed to manuscript preparation and dissemination. CM: Pediatric Pathologist contributed to manuscript preparation and dissemination. JC: Maternal Fetal Medicine Specialist provided case description, and ultrasound images, obtained patient consent, and contributed to manuscript preparation and dissemination. BR: Medical Student contributed to manuscript preparation and dissemination.

ORCID

Brianne Robinson https://orcid.org/0000-0003-0920-7481

REFERENCES

1. Devriendt K. Hydatidiform mole and triploidy: the role of genomic imprinting in placental development. *Hum Reprod*. 2005;1:137-142.
2. Coleman RE, Everard J, Hancock BW, Webster J, Walkington L. Hyperthyroidism and human chorionic gonadotrophin production in gestational trophoblastic disease. *Brit J Cancer*. 2011;104:1665-1669.
3. De Franciscis P, Schiattarella A, Labriola D, et al. A partial molar pregnancy associated with a fetus with intrauterine growth restriction delivered at 31 weeks: a case report. *J Med Case Rep*. 2019;13:1-5.
4. Ross JA, Unipan A, Clarke J, Magee C, Johns J. Ultrasound diagnosis of molar pregnancy. *Ultrasound*. 2018;26(3):153-159.
5. Burton GJ, Jauniaux E. Pathophysiology of histological changes in early pregnancy loss. *Placenta*. 2005;26:114-123.
6. Zaragoza MV, Surti U, Redline RW, Millie E, Chakravarti A, Hassold TJ. Parental origin and phenotype of triploidy in spontaneous abortions: predominance of diandry and association with the partial hydatidiform mole. *Am J Hum Genet*. 2000;66:1807-1820.
7. Toufaily MH, Roberts DJ, Westgate MN, Holmes LB. Triploidy: variation of phenotype. *Am J Clin Pathol*. 2016;145:86-95.

8. Ngan HY, Seckl MJ, Berkowitz RS, et al. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynaecol Obstet*. 2015;131:S123-126.
9. Nguyen NM, Khawajkie Y, Mechtouf N, et al. The genetics of recurrent hydatidiform moles: new insights and lessons from a comprehensive analysis of 113 patients. *Modern Pathol*. 2018;31:1116-1131.
10. Koc S, Ozdegirmenci O, Tulunay G, et al. Recurrent partial hydatidiform mole: a report of a patient with three consecutive molar pregnancies. *Int J Gynecol Cancer*. 2006;16:884-943.

How to cite this article: Robinson B, Brock J-A, Midgen C, Coolen J. Molar and nonmolar triploidy: Recurrence or bad luck. *Clin Case Rep*. 2020;8:785–789. https://doi.org/10.1002/ccr3.2703