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CASE REPORT

Twin Pregnancy Presenting with Hydatidiform Mole and Co-existing Living Fetus with Ovarian Venous Thrombosis: A case report

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ABSTRACT

Background: This case was a twin pregnancy with a complete hydatidiform mole (CHM) and a co-existing fetus. Gestational trophoblastic neoplasia (GTN) and ovarian venous thrombosis (OVT) were diagnosed during the postpartum period.

Case: A 25-year-old pregnant woman, gravid 2, para1-0-0-1 presented with vaginal bleeding. Ultrasonography showed multi-cystic placenta separated from a normal placenta and a living fetus. The patient had a vaginal delivery at 31^{+5} weeks of gestation. Placental histology described a CHM and negative p57(kip2) immunohistochemistry. Post-molar GTN was diagnosed after one month of delivery. Low-risk GTN was diagnosed with OVT. Clinical symptoms subsided after administrating of single-agent methotrexate and an anticoagulant and without complication during one year follow-up.

Conclusion: CHM with a co-existing fetus needs imaging, prenatal genetics, and pathological plus p57(kip2) immunohistochemistry for diagnosis.

Keywords: molar pregnancy, trophoblastic disease, co-existing normal fetus, venous occlusion.

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ตั้งครรภ์แฝดร่วมกับครรภ์ไข่ปลาอุกและมีภาวะลิ่มเลือดอุดตันเส้นเลือดดำที่รังไข่หลังคลอด, รายงานผู้ป่วย 1 ราย

คริษฐ์ จายะสกุล, เด่นศักดิ์ พงศ์โรจน์เผ่า, อวัสดา บุณยัษเฐียร, อารยา สามหมอ, อธิตา จันทเสนานนท์, คมสันติ์ สุวรรณฤกษ์

บทคัดย่อ

ผู้หญิงตั้งครรภ์อายุ 25 ปี ตั้งครรภ์ครั้งที่ 2 มาโรงพยาบาลด้วยเรื่องเลือดออกผิดปกติจากช่องคลอด ตรวจด้วยคลื่นเสียงความถี่สูงพบครรภ์แฝดของทารกที่มีชีวิตและพบลักษณะถุงน้ำปริมาณมากในมดลูกซึ่งแยกออกจากรก ผู้ป่วยคลอดทางช่องคลอดก่อนกำหนดที่อายุครรภ์ 31 สัปดาห์ 5 วัน ผลพยาธิวิทยาของรกวินิจฉัยครรภ์ไข่ปลาอุกและส่งตรวจทางอิมมูโนฮีสโตเคมี P57 ผลเป็นลบ ผู้ป่วยได้รับติดตามหลังคลอด 1 เดือนตรวจพบมะเร็งเนื้อรกที่มีความเสี่ยงต่ำหลังตั้งครรภ์ไข่ปลาอุกและพบภาวะลิ่มเลือดอุดตันเส้นเลือดดำที่รังไข่ ได้รับการรักษาด้วยยาเคมีบำบัดชนิดเดี่ยวเมโธเทรกเซตและยาละลายลิ่มเลือด โดยผู้ป่วยได้รับการติดตาม 1 ปี ไม่พบภาวะแทรกซ้อน

การตั้งครรภ์แฝดร่วมกับครรภ์ไข่ปลาอุกมีโอกาสคลอดครรภ์แฝดที่มีชีวิตพบได้ร้อยละ 50 โดยอัตราส่วน 2 ใน 3 คลอดก่อนกำหนด และมีความเสี่ยงต่อภาวะแทรกซ้อนของมารดาและทารก และความเสี่ยงต่อมะเร็งเนื้อรกมากกว่าการตั้งครรภ์ไข่ปลาอุกเดี่ยว ซึ่งผู้ป่วยควรได้รับคำแนะนำแนวทางการรักษาและความเสี่ยง ภาวะลิ่มเลือดอุดตันเส้นเลือดดำที่รังไข่ในรายที่ไม่มีอาการยังไม่มีการรักษาที่เป็นมาตรฐาน โดยยังเป็นที่อภิปรายระหว่างการให้ยาละลายลิ่มเลือดร่วมกับยาฆ่าเชื้อ การให้ยาละลายลิ่มเลือดอย่างเดียวหรือไม่ได้รับยา

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Introduction

Gestational trophoblastic disease is a spectrum of related diseases originating from abnormal placenta trophoblast proliferation. Pathogenesis arises from abnormal chromosome fertilization between ovum and sperm. The incidence of co-existing twins with complete molar pregnancy is 1:22,000–100,000 pregnancies[1]. Co-existing twin with complete molar pregnancy refers to one chromosomally normal fetus paired with diploid molar pregnancy. Presentation of co-existing twins with complete molar pregnancy includes antepartum bleeding, hyperemesis gravidarum, thyrotoxicosis[2]. If multiple cystic placentae with viable fetus were detected during antenatal ultrasound, the differential diagnosed include co-existing twin with complete molar pregnancy, partial hydatidiform mole or placenta mesenchymal disease. Co-existing twins with complete molar pregnancy increases the rate of medical complications, for instance antepartum hemorrhage, pregnancy induced hypertension, thyrotoxicosis, and preterm delivery[3]. Major congenital anomalies have not been reported[4]. Termination or expectant management is controversial. Intrapartum, vaginal delivery or caesarean section are definitely not delivery route determination. The risk for gestational trophoblastic neoplasia (GTN) increases when compared between co-existing molar with normal pregnancy and singleton molar pregnancy[5]. Postpartum surveillance should monitor beta human chorionic gonadotropin (β-hCG) to detect post molar gestational trophoblastic neoplasia. Contraception is preferable during the monitoring period to prevent confusion in rising β-hCG[4].

The present study reported a structurally normal female fetus co-existing with the abnormal vesicular placenta. The pathology reported complete hydatidiform mole. Nevertheless, the probability of viable fetal outcomes and post-molar GTN rate remains debated. We reviewed previous literature according to this case.

Case report

The patient was a 25-year-old Thai pregnant female, gravida 2, para 1-0-0-1, twenty fourth weeks plus four days of gestational age by last menstrual period confirmed by ultrasound at 16^{+2} weeks. She presented with one-time abnormal uterine bleeding 4 weeks prior to primary hospitalization. Then, she was referred to Maternal Fetal Medicine unit at Thammasat University Hospital. She denied abdominal pain, water broken nor passing tissue. Speculum examination showed minimal bloody discharge and closed cervix. Her pregnancy resulted from natural conception. She denied abnormal past medical nor surgical history. Primary gravida was delivered via vaginal route 4 years ago. The vital signs were normal. The uterus size was 25 centimeters from pubic symphysis. Other findings were within normal limits. The transabdominal ultrasound finding showed a single alive fetus. Fetal anomaly scan was normal. Multiple cystic placentae with normal placenta were detected (Fig. 1) and color doppler flow was performed (Fig. 2). Corpus luteal cyst was not identified. Laboratory investigations were sent. Serum for β-hCG was 195,814 mIU/ml, more than the upper limit of comparable gestational age. The thyroid function test was in range (thyroid stimulation hormone was 1.06 uIU/mL, Thyroxine was 2.54 ng/dL). Amniocentesis was performed. Quantitative fluorescence polymerase chain reaction (QF-PCR) showed diploidy (XX), aneuploidy chromosome 13,18,21 was not detected.

The patient was counseled regarding the possible risk of pregnancy, fetus, and complications and pregnancy was continued. Antepartum care, fetal growth and wellbeing were monitored. Blood pressure was within normal limits. Blood for β-hCG was collected weekly (Fig. 3). The newborn had preterm vaginal delivery at 31^{+5} weeks of gestational age. Her intrapartum blood loss was 1,000 ml from incomplete placental delivery. Suction and curettage were performed. Microscopic description showed a few enlarged villi with focal central cistern and marked trophoblastic proliferation (Fig. 4). Immunohistochemistry p57(kip2) was negative in villous cytotrophoblast and villous stroma. At postpartum serum β-hCG were 598, 240, 608, 1,566 mIU/mL in the follow-up weekly blood sampling. Therefore, post molar gestation trophoblastic neoplasia was diagnosed by rising in β-hCG (Fig. 5).

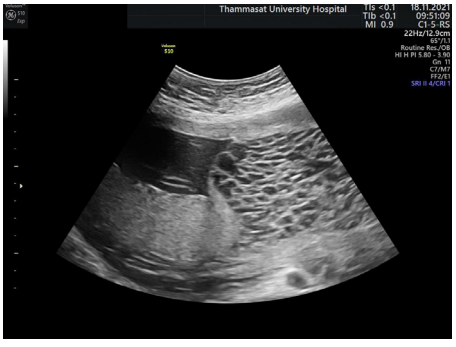

Fig. 1. Transabdominal ultrasound shown multiple cystic placentae with normal placenta.

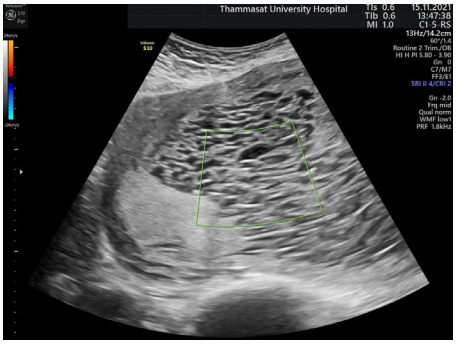

Fig. 2. Transabdominal ultrasound shown multiple cystic placentae with absent color doppler flow.

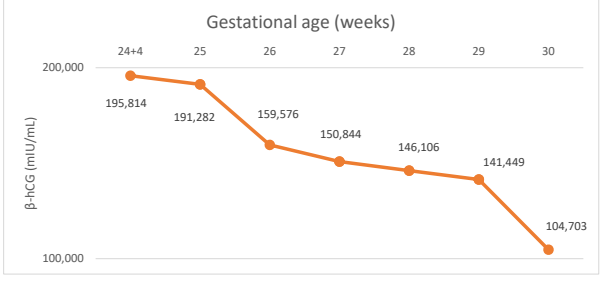

Fig. 3. Blood for antepartum B-hCG level.

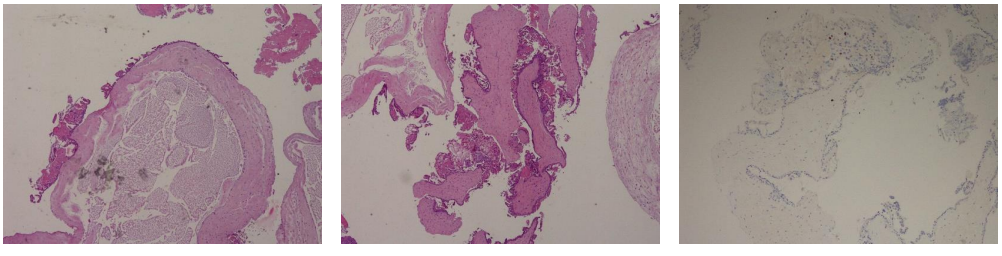

Fig. 4. Microscopic description shows a few enlarged villi with focal central cistern and marked trophoblastic proliferation. Immunohistochemistry P57 was negative in villous cytotrophoblast and villous stroma.

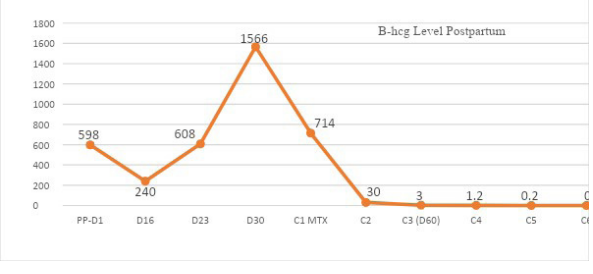

Fig. 5. Beta- human chorionic gonadotropin level, PP-D1: postpartum day 1, C1 MTX: 1st cycle of methotrexate.

Computed tomography (CT) showed no distant metastasis. Bilateral ovarian vein thromboses (OVT) were detected. The International Federation of Gynecology and Obstetrics (FIGO) stage was 1. The World Health Organization scoring system, also known as FIGO score, was 3 points. The single-agent chemotherapy (methotrexate) was administered. The β-hCG level declined to normal within three cycles of chemotherapy, and two additional courses were administrated. Low molecular weight heparin (LMWH) was administrated along with chemotherapy. After six months of anticoagulant treatment, an abdominal CT venogram reported decreased size and extension of venous thrombosis at the right ovarian vein. Complete recanalization of the right ovary without clinical symptoms was found. A left ovarian vein and other venous vessels were intact with no filling defect. During one year follow-up, condom was used as a contraceptive method and menstrual cycle was regular interval. The preterm newborn was born with birthweight 1,500 gram with Apgar score 8,10 and stayed at the hospital for 1 month before discharged (Fig. 6).

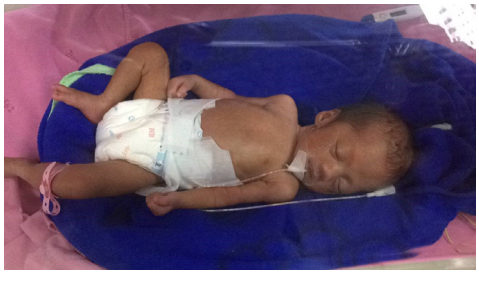

Fig. 6. The preterm newborn was born with birthweight 1,500 gram with Apgar score 8,10.

Discussion

Gestational trophoblastic disease covers both benign and malignancy diseases. Benign conditions include complete hydatidiform mole and partial hydatidiform mole, while GTN, a malignant condition, includes post-molar GTN, invasive mole, choriocarcinoma, placenta site trophoblastic tumor, and epithelioid trophoblastic tumor[4]. Co-existing fetus with complete mole (normal fetus with mole placenta) is a very rare condition. This is the first case of coexisting fetus with complete mole at Thammasat University Hospital.

During prenatal ultrasonography, detecting complex cystic placenta with normal fetus is challenging. The differential diagnoses are co-existing twin with complete mole, partial mole, and placental mesenchymal dysplasia (PMD). Co-existing twins with complete mole may show normal viable fetus. However, both PMD and partial hydatidiform mole may be associated with fetal abnormality, such as fetal growth restriction and Beckwith-Wiedemann syndrome in PMD[6]. McNally reported that blood β–hCG above 200,0000 IU/L was found in coexisting fetus with mole[7].

Histology can be helpful to differentiate hydatidiform mole and PMD. When comparing histology, hydatidiform mole consists of trophoblastic hyperplasia, while trophoblastic dysplasia is not found in PMD[6]. Immunohistochemistry (p57 (kip2)) is used to detect paternal genes, which are positive in partial mole[4]. Meanwhile, trophoblastic proliferation with p57(kip2) negative was reported in cytotrophoblasts and villous stroma. In this subject, co-existing twins with complete molar pregnancy was confirmed.

Some reports had proposed the selective use of other essays, such as fluorescence in situ hybridization (FISH), microsatellite genotype, or single nucleotide polymorphism (SNP) -microarray analysis, to clarify the diagnosis[8]. Fetal karyotype should be performed during prenatal diagnoses such as chorionic villus sampling, maternal cell-free deoxyribonucleic acid (DNA) testing, or amniocentesis

according to gestational age[8, 9].

The previous reports were summarized and presented in Table 1. Morbidity and mortality in current pregnancy included antepartum hemorrhage (60-70%), pregnancy induce hypertension (15.30%), thyrotoxicosis (15-25%), pulmonary edema (10%), and postpartum hemorrhage (10%)[1, 2, 10, 11]. In 2020, Sharon reported eighty percent of twin pregnancies with obstetric complications[2]. In Suksai's review literature, one-third (66/183) subjects required termination of pregnancy due to maternal complications[11]. Thus, maternal complications must be advised. The choice of management between continuation of pregnancy and termination of pregnancy would be determined. In Irani's study, there was no subject with term delivery (0/14), while 5/14 subjects had preterm delivery. Lin et al in 2017 reported 72 coexisting twins with molar pregnant woman; ten of which chose elective termination, while 60 decided to continue with pregnancy. During follow-up antenatal care among conservative pregnancies, the subjects had delivered 25 preterm and 11 term newborns. Twelve (7/60) percent ended the pregnancy with termination due to maternal complication. Lin suggested that the risk for developing subsequent post molar GTN was not significant between subjects who chose continued pregnancy and elective termination.

Table 1. Clinical presentation.

	Sharon NZ, 2020	**Lin LH, 2017**	**Irani RA, 2021**	**Present Study**
Literature	Systematic	Retrospective	Review	Case
number of cases	244	72	14	1
Incidence	1/22,000-100,000			NA
Diagnosis GA*	12-23	15 (9-30)	12 (9-19)	24
Median B-hcg	NA	400,000	355,494	195,814
Abortion vs Pregnancy (%)	25.4 vs 74.6	13.9 vs 83.3	21.0 vs 63.3	Pregnancy
Obstetrics complication (%)				
Vaginal bleeding	70.5	59.0	71.0	Yes
Preeclampsia	14.3	32.0	28.9	No
Hyperthyroid	23.5	14.0	0.7	No
RDS	NA	9.7	0.7	No
Fetal viability	50.0	60.0	55.6	Yes
Preterm	78.0	69.0	100.0	31 weeks
IUFD	40.1	28.0	NA	No
Overall complications	80.8	63.0	NA	No
Post-molar GTN (%)	34.0	46.0	28.6	GTN

* mean (range) weeks
GA: gestational age, β-hcg: beta- human chorionic gonadotropin, RDS: respiratory distress syndromes such as pulmonary embolism or pulmonary edema, IUFD: intrauterine fetal death, GTN: gestational trophoblastic neoplasia, NA: not available

In most cases delivery via cesarean route due to preeclampsia with a severe feature, hemolysis, suspected invasive moles and abnormal fetal presentation[5, 7, 10, 12]. The presenting case delivered by vaginal delivery without severe complications. Postpartum surveillance should monitor β-hCG the

same as hydatidiform mole[4]. Diagram for management is shown in Fig. 7. The route of delivery remains controversial. Nonetheless, elective caesarean section is not recommended.

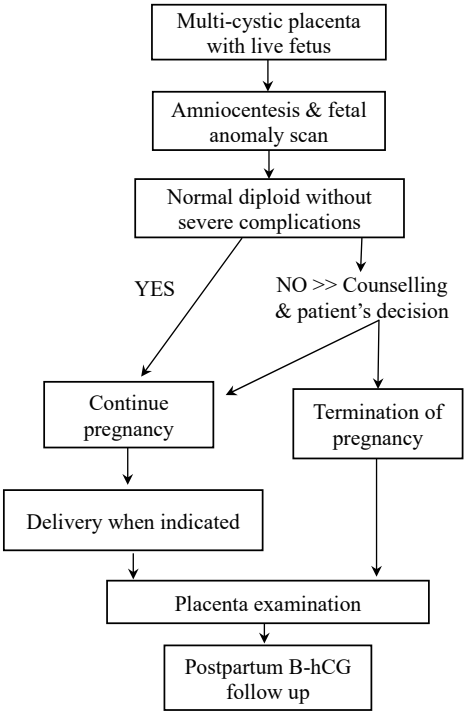

Fig. 7. Diagram for management multi-cystic placenta with a live fetus[7,10,12].

The risk of postpartum post molar GTN is 28.6-46%[1, 2, 7, 10] which is higher than those of complete and partial mole: 7-30 and 2.5-7.5%, respectively[4]. Blood for β–hCG should be monitored. Oral contraception is recommended to suppress endogenous luteinizing hormone (LH) and follicle stimulating hormone (FSH)[4].

Ovarian venous thrombosis (OVT) is a rare condition. The typical symptoms were abdominal pain, fever, and palpable mass[13]. Imaging modalities for diagnosis were the ultrasound (US), CT, and magnetic resonance imaging (MRI). In a systematic review, the sensitivity and specificity for the diagnosis by the US were 50-100% and 41-99%, respectively. Sensitivity and specificity of CT were 70-100% and 62-99%, respectively. The best investigation was MRI, with nearly 100% sensitivity and specificity[13]. This study incidentally identified bilateral OVT from a metastatic workup without clinical symptoms. The ovarian thrombus can extend to major vessels such as inferior vena cava (15%), renal vein (12%), and pulmonary vein (10%)[14, 15]. Riva et al reported risk factors of OVT were malignancy, postpartum, oral contraceptive pills, pelvic surgery, and pelvic infection. Treatment of OVT is controversial. There are three options from the previous literature. First, a combination of antibiotics and anticoagulants was administered. The board-spectrum antibiotics should be medicated until the fever resolved at least 48 hours. Anticoagulant was administered for 1 to 3 months, according to the Canadian Society of Obstetrics and Gynecologists 2014[16]. Second, only anticoagulant was administered for 3 to 6 months according to the guidelines of the British Committee for Standards in Hematology 2012[17]. Third, no treatment in asymptomatic incidentally detected isolated OVT in a patient with malignancy[17]. The extent of anticoagulation duration varies between 3 to 6 months with LMWH, oral

anticoagulant, or vitamin K antagonist[13]. OVT in post-molar GTN is rare condition, only one case report was evident by KIM et al,[18] In this study, an incidental OVT was diagnosed along with post-molar GTN. LMWH administered the treatment for 6 months. The clinical subsided without complications such as premature ovarian failure, renal failure and pulmonary embolism.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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