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Hereditary haemorrhagic telangiectasia with atrial septal defect and pulmonary hypertension during advanced pregnancy: a case report and literature review

Shouze Liu[1,*], Qianqian Zhang[1,*], Wenhua Liu[2], Lili Zheng[1], Jingwen Zhou[1] and Xianghua Huang[1]

Abstract

Pregnancy complicated with hereditary haemorrhagic telangiectasia (HHT) is a rare condition. This case report presents an extremely rare case with the co-occurrence of HHT and congenital heart disease. In this report, a 43-year-old woman at 36 + 4 weeks of gestation experienced haemoptysis with a volume of approximately 300 ml for the first time. Uncommonly, her transthoracic echocardiogram revealed a previously unrecognized atrial septal defect (ASD) and pulmonary hypertension (PH) for the first time at 36 + 1 weeks of gestation. Chest computed tomography revealed an arteriovenous malformation (AVM) in the right lower lobe of the lung. Due to concerns of rebleeding of ruptured pulmonary arteriovenous malformations (PAVMs), the patient underwent a caesarean section at 36 + 6 weeks of gestation. A healthy male infant weighing 2800 g was delivered. To the best of our knowledge, there have been few reports about HHT with ASDs and PH during advanced pregnancy. This current case report highlights the necessity for clinicians to pay considerable attention to cardiac structural abnormalities, which can worsen PAVM in patients with HHT during pregnancy, for whom terminating the pregnancy in time may reduce the risk of PAVM rupture.

[1]Department of Gynaecology and Obstetrics, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China
[2]Department of Pain, Cangzhou Hospital of Integrated TCM-WM Hebei, Cangzhou, Hebei Province, China

*These authors contributed equally to this work.

Corresponding author:
Xianghua Huang, Department of Gynaecology and Obstetrics, The Second Hospital of Hebei Medical University, 215 Heping West Road, Shijiazhuang, Hebei 050011, China.
Email: xianghuahuang0311@163.com

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Introduction

Hereditary haemorrhagic telangiectasia (HHT) is a relatively common autosomal dominant genetic disorder with a prevalence of 1:5000 to 1:8000.[1] Due to a lack of capillary beds, there is an abnormal direct connection between arterioles and venules. Existing in different locations in the body, these strange structures can lead to various clinical manifestations. At present, it is believed that HHT is commonly associated with recurrent nose bleeds, cutaneous telangiectasia and arteriovenous malformation (AVM), which usually occur in the liver, lungs and central nervous system.[2] This condition is rarely seen in pregnancy, and reports of simultaneous atrial septal defects (ASDs) and pulmonary hypertension (PH) during pregnancy are even rarer.[1]

Pregnancy, as a consequence of the associated hormonal and haemodynamic changes, not only can have an impact on HHT,[3] but it can also reveal pre-existing coronary heart disease.[4] In addition, these heart problems severely exacerbate blood shunting through AVMs, leading to the rupture of already abnormal blood vessels.[5]

This current case report describes a novel case of a previously unrecognized ASD and PH complicated with HHT during advanced gestation. These newly diagnosed structural abnormalities of the heart made a difference to HHT. Ultimately, the patient experienced haemoptysis with a volume of approximately 300 ml at 36 + 4 weeks of gestation. In order to avoid further bleeding, the patient underwent caesarean section at 36 + 6 weeks of gestation and a healthy male infant was born.

Case report

In October 2020, a 43-year-old female patient, gravida 2, para 1, at 36 weeks of gestation, was admitted in stable condition to Department of Obstetrics, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China following the diagnosis of placenta accreta for 1 month. She experienced her first haemoptysis of approximately 300 ml on the morning of the 4th day of admission. She denied haemoptysis prior to this event but gave a history of recurrent spontaneous epistaxis for more than 30 years.

Maternal vital signs revealed a blood pressure of 133/73 mmHg, heart rate of 97 bpm and her oxygen saturation level was 98% on room air. She denied any history of exposure to radioactive or toxic substances or drug use. Her previous obstetric history was relevant for an uncomplicated term caesarean delivery to a healthy infant 15 years ago. On physical examination, telangiectasias were found on the skin of her forearm (Figure 1). There were no scattered bleeding spots or ecchymosis throughout her body. Chest computed tomography (CT) revealed an AVM in the right lower lobe of the lung (Figure 2). No abnormalities were found in craniocerebral CT. Transabdominal ultrasound showed diffuse hepatic artery dilatation (Figure 3). CO was

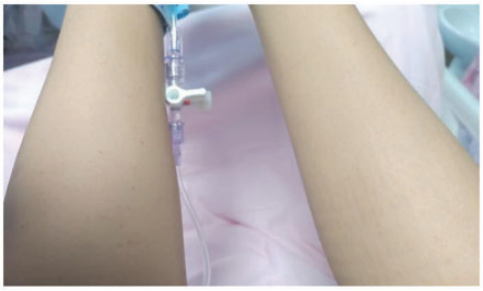

Figure 1. The subsequent physical examinations of a 43-year-old female patient, gravida 2, para 1, at 36 weeks of gestation, admitted in a stable condition following the diagnosis of placenta accreta for 1 month, revealed telangiectasias on the skin of her forearm. The colour version of this figure is available at: http://imr.sagepub.com.

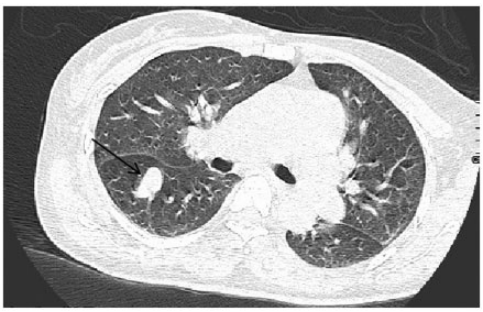

Figure 2. Computed tomography of the chest of a 43-year-old female patient, gravida 2, para 1, at 36 weeks of gestation, admitted in a stable condition following the diagnosis of placenta accreta for 1 month, demonstrated right lower lobe arteriovenous malformation (black arrow).

6.31 l/min estimated with transthoracic echocardiogram, which also revealed an ASD, an elevated pulmonary systolic blood pressure of approximately 42 mmHg, a dilated pulmonary artery (27 mm) and an abnormal eccentricity index (EI) for the first time at 36 + 1 weeks of gestation (Figure 4). However, these were not found during her last test at 30 + 1 weeks of gestation. Except for hypoproteinaemia, routine blood tests including haemoglobin and haematocrit, comprehensive metabolic panels and

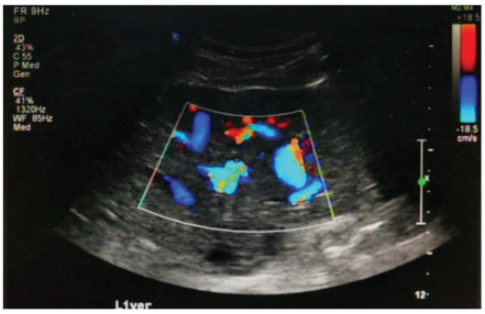

Figure 3. Transabdominal ultrasound examinations of a 43-year-old female patient, gravida 2, para 1, at 36 weeks of gestation, admitted in a stable condition following the diagnosis of placenta accreta for 1 month, revealed diffuse hepatic artery dilatation. The colour version of this figure is available at: http://imr.sagepub.com.

coagulation tests were within normal limits. Her clinical presentation and imaging characteristics were consistent with HHT.

Haemoptysis stopped after haemostatic treatment with haemocoagulase injection (intravenous injection 1 unit + intramuscular injection 1 unit). Even so, there were concerns about rebleeding of ruptured pulmonary arteriovenous malformations (PAVMs). The patient underwent a caesarean section at 36 + 6 weeks of gestation. A male infant weighing 2800 g was delivered with Apgar scores of 9 and 10 at 1 and 5 min. The patient was discharged 1 week later, during which no recurrent haemoptysis occurred. She and her baby were continuously followed up by telephone for 6 months and they remained well without any complications. The reporting of this study conforms to CARE guidelines.[6] Written informed consent forms for publication of this article and treatment were obtained from the patient. All of her information remained anonymous.

Discussion

As an autosomal dominant hereditary disease, HHT is characterized by recurrent

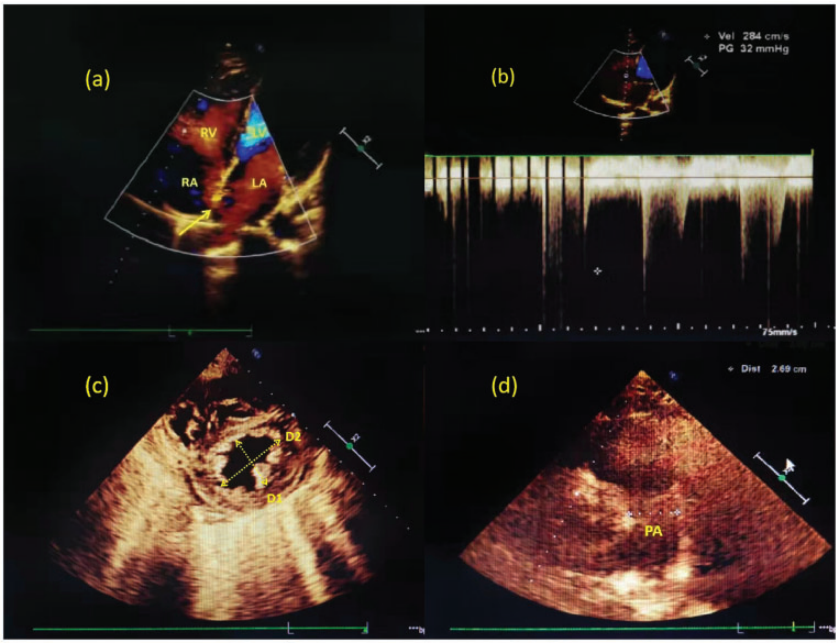

Figure 4. Transthoracic echocardiogram of a 43-year-old female patient, gravida 2, para 1, at 36 weeks of gestation, admitted in a stable condition following the diagnosis of placenta accreta for 1 month, demonstrated the following: (a) an atrial septal defect. The yellow arrow indicates that blood flowed through the opening in the septum (LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle); (b) estimated systolic pulmonary artery pressure; (c) an eccentricity index (EI) of 1.4 where EI = D2/D1 (D1, left ventricular diameter perpendicular to the septum; D2, left ventricular diameter parallel to the septum; (d) a dilated pulmonary artery (PA); The white dotted line represents the pulmonary artery diameter. The colour version of this figure is available at: http://imr.sagepub.com.

spontaneous epistaxis, cutaneous telangiectasia and AVMs.[7] PAVMs are commonly present in about 50% of HHT women.[8] This current patient, an atypical pregnant woman with HHT that was complicated with previously unrecognized ASD and PH, developed massive haemoptysis in the third trimester of pregnancy. Indeed, her relevant past history indicated a smooth childbirth 15 years ago, when the echocardiogram showed no abnormality. And there were no serious complications except for the symptoms of epistaxis, so no systematic screening was performed for HHT during or after her first pregnancy. Fortunately, with advancing insight in this disease and the refinement of guidelines, the probability of a missed diagnosis is decreasing. Moreover, although embolization of PAVM was a fast and simple procedure to save the mother's life, the patient was not diagnosed with HHT until the occurrence of haemoptysis, that was, at 36 + 4 weeks of gestation. As a result, there was no intervention in PAVM before. In addition, considering the rise of pulmonary artery pressure, we believe that reducing circulatory load was the best way to reduce the risk of PAVM rupture. On the contrary, PAVM embolization might make PH worse, resulting in fatal maternal and foetal outcomes. However, the patient refused further surgery after the pregnancy. Fortunately, both were in good condition during

follow up. To the best of our knowledge, there have been few reports about HHT with ASD and PH during advanced pregnancy.[1]

Since the first report of a case of multiple pulmonary arteriovenous fistulas during pregnancy in women complicated with HHT in 1986, 24 cases with serve complications during pregnancy have been published as case reports (Table 1). [3,9–29] The gestational weeks of the adverse events range from 10 to 36 weeks. The most common complications were associated with PAVMs. Seven women had acute PAVM-related haemoptysis;[12,13,16,17,23,24,29] and among them, four occurred in the third trimester. This indicates that PAVM-related haemoptysis seems to be connected with increased cardiac output. This was consistent with the current case report. Although two patients presented with PH estimated with transthoracic echocardiogram,[21,22] this was considered to result from the increased cardiac output caused by hepatic AVMs. In the current case, a transabdominal ultrasound showed diffuse hepatic artery dilatation. Reviewing her medical examination, PH occurred secondary to both ASD and hepatic arteriovenous dilatation.

As HHT is a systemic disease, the treatment varies according to the location of the lesion. It mainly includes transfusion,[10,15,27] surgery,[9,11,14,15,17,18,27] embolization,[12,13,17,20,23–26,28] drainage[15,16,18,26] and diuresis.[10,12,13,21,22] Although three of the previous cases had been diagnosed with HHT and treated for PAVMs before pregnancy, recanalization of PAVMs occurred, partly as a result of pregnancy, accompanied by subsequent haemoptysis.[17,23,24] Ten women finally underwent caesarean delivery with gestational age ranging from 20 to 40 weeks, and among them, one maternal death occurred due to massive intra-abdominal haemorrhage with multiple AVMs in the gastrointestinal tract.[20] Two women with haemoptysis eventually gave birth to living infants via spontaneous vaginal delivery.[23,24] In the present case, the patient was not diagnosed with HHT until $36+1$ weeks of gestation and had not received treatment for PAVMs, so continuing her pregnancy might have lead to a fatal maternal outcome, so the pregnancy was terminated by caesarean section. It has been reported that life-threatening events occurred in 2.7 to 6.8% of pregnancies.[30–32] Furthermore, a large cohort study has shown that compared with women previously considered well, there was an improved survival rate in pregnancies with a prior diagnosis of HHT at the time of pregnancy.[30] This means that, in women with known HHT, specific medical supervision during pregnancy is needed.

At present, it is believed that the occurrence of HHT is related to mutations in the ENG,[33] *ACVRL1*[34] and *SMAD4*[35] genes, which upset the balance between proangiogenic factors and antiangiogenic factors. Pregnancy promotes modification of the vascular bed through related hormonal changes.[36] It can affect the disease due to systemic vasodilatation and a progressive decrease in peripheral vascular resistance (PVR).[37] The decrease in PVR creates a relatively underfilled vascular state, which may lead to an increase in plasma volume to respond to the relative vascular underfill.[38] The plasma volume expands rapidly until week 34, after which there is only a modest increase.[38] Concurrently, there is an increase in cardiac output (CO), which can increase by up to 45% during the first trimester.[39] These changes in plasma volume and CO during pregnancy contribute to the increased risk of cardiac complications in women with pre-existing heart disease.[4] Meanwhile, haemodynamic changes aggravate the shunting of blood through the abnormal vascular bed in women with HHT.[40] Consequently, there

Table 1. Severe complications occurring during pregnancy in women with hereditary haemorrhagic telangiectasia (HHT) reported since 1986.[3,9–29]

Related lesions	Authors	Treatment before pregnancy	The GA of events, weeks	Complications	Symptoms	Therapy	Date of delivery	Maternal and fetal outcomes
PAVM	Swinburne et al. 1986[9]	Right lower and middle lobectomy	35	Hypoxaemia	Fatigue, dyspnoea	Post-partum bilateral lung wedge resections	35 (CS)	A limited life A healthy infant
HAVM	Livneh et al. 1988[10]	–	24	High output heart failure	Dyspnoea, oedema	Transfusion, diuresis	35 or later (VD)	Symptomless A healthy infant
HAVM	Livneh et al. 1988[10]	–	26	High output heart failure	Dyspnoea, oedema	Diuresis	40	Recovered A healthy infant
CAVM	Neau et al. 1988[11]	–	30	Intracranial haemorrhage	Hemiplegia with aphasia, headache and vomiting	Craniotomy	30 (VD)	Both had fatal outcomes
PAVM	Gammon et al. 1990[12]	–	24	Hypoxaemia, haemothorax	Chest pain, dyspnoea and haemoptysis	Diuresis, embolization	30 (VD)	Recovered well A healthy infant
PAVM	Waring et al. 1990[13]	–	26	Hypoxaemia, haemothorax	Dyspnoea, haemoptysis	Diuresis, embolization	32 (VD)	Recovered A healthy infant
PAVM	Laroche et al. 1992[14]	–	29	Haemothorax, circulatory collapse	Dyspnoea, chest pain	Partial lobectomy	39 (CS)	Recovered well A healthy infant
PAVM	Freixinet et al. 1995[15]	–	25	Haemothorax, hypovolaemic shock	Dyspnoea	Drainage, transfusion and fistulectomy	27 (CS)	Satisfactory A live infant
PAVM	Adegboyega et al. 1996[16]	–	30	Haemothorax	Haemoptysis, chest pain	Drainage	40 (CS)	Relapsed 13 years later A healthy infant
PAVM	Wispelaere et al. 1996[17]	Embolization	10	Severe haemoptysis	Haemoptysis, loss of consciousness	Re-embolization, partial lobectomy	–	Induced abortion
PAVM	Jakobi et al. 2001[18]	Partial lobectomy	25	Hypoxaemia	Cyanosis	–	25	– Fetal death
PAVM	Jakobi et al. 2001[18]	–	26	Haemothorax	–	Drainage, thoracotomy	40 (VD)	Recovered uneventfully SGA infant
PAVM	Worda et al. 2007[19]	Upper left lobectomy	12	Hypoxaemia	Cyanosis, dyspnoea	–	32 (CS)	Both were in good condition

(continued)

Table 1. Continued.

Related lesions	Authors	Treatment before pregnancy	The GA of events, weeks	Complications	Symptoms	Therapy	Date of delivery	Maternal and fetal outcomes
PAVM HAVM GAVM	Sivarani et al. 2010[20]	–	36	Active pulmonary haemorrhage, gastrointestinal bleeding	High-output cardiac failure	Emergent embolization	36 (CS)	Died of massive intra-abdominal haemorrhage A live infant
HAVM	Lai et al. 2010[21]	–	36	High-output cardiac failure	Dyspnoea	Diuresis	36 (CS)	Recovered to NYHA functional class 2 A live infant
HAVM	Berthelot et al. 2015[22]	–	25	High-output cardiac failure	Dyspnoea, itch and lower limb oedema	Diuresis	33 (CS)	Recovered after 3 months A healthy infant
PAVM	Tandon et al. 2017[23]	Coil embolization	32	Hypoxaemia	Haemoptysis, syncope	Embolization with balloon and recoiling	33 (VD)	Recovered A healthy infant
PAVM	Yaniv-Salem et al. 2017[24]	Embolization	35	Haemoptysis	Massive haemoptysis	Re-embolization	37 (VD)	Recovered A live infant
RAVM	Askim et al. 2018[25]	–	12	Branch retinal artery occlusion	Defect of visual field	Anticoagulant, coil embolization	40 (VD)	Recovered A live infant
PAVM	Raiya et al. 2017[26]	–	23	Haemothorax	Sudden chest pain, breathlessness, cough	Pleural aspiration, coil embolization	40 (–)	Recovered A healthy infant
PAVM	Texier et al. 2018[27]	–	26	Haemothorax	Chest pain	Transfusion, surgery	40 (VD)	Recovered A healthy infant
PAVM, HAVM	Md Noh et al. 2018[28]	–	20	Haemothorax, rectal bleeding	Dyspnoea	Coil embolization	20 (CS)	Recovered Intrauterine fetal death
PAVM	Banerjee et al. 2018[29]	–	34	Haemoptysis	Haemoptysis	–	–	Recovered –
PAVM	Borovac-Pinheiro et al. 2019[3]	–	14	Hypoxaemia	Dyspnoea	–	34 (CS)	A limited life A healthy infant

GA, gestational age; PAVM, pulmonary arteriovenous malformation; CS, caesarean section; HAVM, hepatic arteriovenous malformation; VD, vaginal delivery; CAVM, cerebral arteriovenous malformation; SGA, small for gestational age; GAVM, gastrointestinal arteriovenous malformation; NYHA, New York Heart Association.

is an enormous risk of AVMs rupture in the third trimester of pregnancy.

In this current case report, echocardiography in the early third trimester did not indicate the existence of shunts, although the patient was complicated with ASD. A progressive rise in blood volume not only played a pivotal role in the occurrence of PH, but also exposed the shunt from left to right with an extension of the gestational age. In addition, the ASD played an additional part in the development of PH, as the shunt from left to right may increase pulmonary blood flow.[41] PH can complicate many cardiovascular and respiratory diseases and is defined as a resting mean pulmonary arterial pressure of $\geq$25 mmHg.[42] Termination of pregnancy will relieve PH complications. However, the risk of imminent major haemorrhage is substantial as long as PAVMs are perfused at systemic pressure due to marked PH of any cause.[43] Unfortunately, we did not terminate the pregnancy in time to remove the factors of PAVM rupture, resulting in massive haemoptysis.

In conclusion, previously unrecognized ASD and PH are risk factors for PAVM rupture in pregnant women complicated with HHT, especially in the late third trimester. As recommended in the current guidelines,[2] screening for PAVM starts with transthoracic contrast echocardiography, which can reveal masked coronary heart disease. This current case report highlights the necessity for clinicians to pay considerable attention to cardiac structural abnormalities, which can worsen PAVM in patients with HHT during pregnancy, for whom terminating the pregnancy in time may reduce the risk of PAVM rupture.

Author contributions

Shouze Liu and Qianqian Zhang contributed to the drafting of the manuscript and approved the final draft. Wenhua Liu, Lili Zheng and Jingwen Zhou prepared figures and approved the final draft. Xianghua Huang critically revised the manuscript for important intellectual content and approved the final draft.

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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ORCID iDs

Shouze Liu https://orcid.org/0000-0003-0932-0409

Xianghua Huang https://orcid.org/0000-0002-0104-4318

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