Recurrent Massive Perivillous Fibrin Deposition Treated with Aspirin and Enoxaparin: A Case Report

Baillie Bronner[1], Margaret Schermerhorn[1], Juliana Sung[1], Anna McCormick[1], and Sam de los Reyes[1]

[1]Rush University Medical Center

November 30, 2022

Manuscript title:

Recurrent Massive Perivillous Fibrin Deposition Treated with Aspirin and Enoxaparin: A Case Report

Short title

Massive Perivillous Fibrin Deposition - Aspirin and Enoxaparin

Authors:

Baillie A. Bronner, MD

Department of Obstetrics & Gynecology Rush University Medical Center (1620 W Harrison St, Chicago IL, 60612)

Margaret Schermerhorn, BS

Rush University Medical College (1620 W Harrison St, Chicago IL, 60612)

Anna McCormick, DO

Department of Maternal Fetal Medicine

Rush University Medical Center (1620 W Harrison St, Chicago IL, 60612)

Juliana Sung, MD

Department of Maternal Fetal Medicine

Rush University Medical Center (1620 W Harrison St, Chicago IL, 60612)

Samantha de los Reyes, MD

Department of Maternal Fetal Medicine

Rush University Medical Center (1620 W Harrison St, Chicago IL, 60612)

Corresponding Author:

Baillie A. Bronner, MD

Department of Obstetrics & Gynecology

Rush University Medical Center (1620 W Harrison St, Chicago IL, 60612)

Email: Baillie_ a_ bronner@rush.edu

Phone number: 505-366-7122

Abstract

Background

Massive perivillous fibrin deposition (MPVFD) is a potentially devastating pregnancy complication that occurs in 0.03-0.5% of deliveries and is associated with severe fetal growth restriction, stillbirth (IUFD), and neurologic injury due to uteroplacental insufficiency[1,2]. Management of patients with recurrent pregnancy loss secondary to MPVFD has not been widely studied.

Case

We describe the case of a healthy 19-year-old with a history of two prior intrauterine fetal demises at 35w6d and 36w6d secondary to MPVFD of the placenta with subsequent delivery of a healthy infant at 33w6d with treatment in the prenatal period with aspirin and prophylactic enoxaparin dosing.

Conclusion

Antenatal treatment with daily aspirin and prophylactic enoxaparin as well as close antenatal follow-up may be an option for patients with recurrent pregnancy loss due to MPVFD.

Main BodyText

Case

We present the case of a 19-year-old G3P0301 with pregnancies complicated by MPVFD of the placenta resulting in two third trimester IUFDs with subsequent delivery of healthy, late preterm infant with treatment during the prenatal period.

In the patient's first pregnancy, prenatal course was largely unremarkable. Past medical and surgical history was only significant for mild persistent asthma. The patient's prenatal labs were significant only for rubella and varicella non-immunity. The patient ultimately presented at 35w6d for labor and was subsequently diagnosed with an intrauterine fetal demise (IUFD). The patient underwent induction of labor and had an uncomplicated spontaneous vaginal delivery. On autopsy, the fetal exam was notable for maceration and organs small for gestational age. There were no signs of intrauterine infection. However, placental pathology was notable for MPVFD covering 75% of the placenta. Infectious workup and antiphospholipid (APLS) testing were negative, and the patient had no signs or symptoms of preeclampsia.

The patient was then seen for a new obstetric visit at a community clinic for the second pregnancy two months after the previous delivery. This pregnancy was complicated by an initial body mass index of 40 kg/m^2 and asthma but was otherwise unremarkable. The patient ultimately transferred care to a tertiary care facility at 31 weeks and was referred to Maternal Fetal Medicine (MFM). The patient was subsequently seen at 36w6d for prenatal care however, the patient had not yet been seen in MFM clinic nor had antepartum testing at this time, so was then immediately sent to MFM clinic for a biophysical profile (BPP) and growth ultrasound. At that time, the fetus was found to have severe fetal growth restriction with reverse end diastolic flow and reverse ductus venosus flow. Fetal heart tones were additionally noted to be in the 90s. The patient was then taken immediately to labor and delivery triage where no fetal heart tones were auscultated and an IUFD was diagnosed. The patient then underwent induction of labor and had a vaginal delivery of a grossly normal appearing male fetus. Hemoglobin A1c, APLS, infectious and preeclampsia work-up was performed and was negative. Pathology showed a placenta that was small for gestational age with multifocally firm areas with increased intervillous fibrin and infarct, again consistent with MPVFD.

For the third pregnancy, the patient had an initial prenatal visit at 8w1d and subsequently established care with MFM at 11w4d. The patient was counseled on treatment options based on few available case reports including primarily thrombolytic therapies (aspirin, heparin) with or without combining immunologically directed treatments [e.g., intravenous immunoglobulin therapy (IVIG)]. The patient ultimately opted for treatment with aspirin 81 mg and enoxaparin 40 mg daily in addition to maternal serum alpha-fetoprotein

testing, serial growth ultrasounds every 4 weeks beginning at 20w0d and weekly BPPs starting at 32w0d. Delivery was recommended between 34w0d-36w0d with betamethasone administration prior. The patient received betamethasone at 33w4d and 33w5d for planned delivery at 34w0d. However, while at antenatal testing at 33w5d, the patient was sent to labor and delivery triage for induction of labor due to a BPP of 6/8, minus two for gross movement. Ultimately, the patient delivered a live male infant via cesarean section at 33w6d for recurrent late decelerations unresolved with resuscitative measures in the setting of prolonged rupture of membranes after a 26-hour induction of labor. Apgar scores were 7 and 9 at 1 and 5 minutes respectively. Placental pathology again showed increased intervillous fibrin, intervillous thrombus, and calcifications (Figure 1) in addition to gross description with pink-yellow, rubbery tissue comprising approximately 90% of the total placental volume consistent with recurrent MPVFD (Figure 2). The infant was admitted to the neonatal intensive care unit secondary to prematurity and was ultimately discharged home on day of life 23. The infant was seen for a 2-month checkup and was noted to be doing well with appropriate growth and development. The patient was seen for a postpartum visit and was additionally noted to be doing well from a postpartum standpoint.

Discusssion

The etiology for MPVFD remains unknown but it can recur in future pregnancies (12-78% reported[8]) as was the case in our patient. The pathogenesis remains unclear, but there is some evidence to suggest that a maternal autoimmune or alloimmune condition may be contributory. Treatment modalities have been reported with some success including primarily thrombolytic therapies (aspirin, heparin) with or without combining immunologically directed treatments (e.g., IVIG, prednisolone)[1,9]. One report notes a live birth with normal postnatal follow-up at 2 years in a woman with a history of four consecutive losses presumably all due to MPVFD who was treated with a combination of thrombolytic therapy (aspirin and heparin), IVIG, and pravastatin to correct the angiogenic/antiangiogenic imbalance thought to be causational of recurrent MPVFD[10]. These reports of isolated successes, but also failures, with a variety of treatments, are not without concerns and there is need for further study.

Based on the success in the case reported here with recurrent MPVFD, we propose treatment with daily aspirin and prophylactic enoxaparin dosing in addition to close follow-up and frequent antepartum testing in patients with a history of MPVFD.

References

1. Abdulghani S, Moretti F, Gruslin A, Grynspan D. Recurrent Massive Perivillous Fibrin Deposition and Chronic Intervillositis Treated With Heparin and Intravenous Immunoglobulin: A Case Report. *J Obstet Gynaecol Can JOGC J Obstet Gynecol Can JOGC*. 2017;39(8):676-681. doi:10.1016/j.jogc.2017.03.089

2. Heller DS, Tellier R, Pabbaraju K, et al. Placental Massive Perivillous Fibrinoid Deposition Associated with Coxsackievirus A16—Report of a Case, and Review of the Literature. *Pediatr Dev Pathol*. 2016;19(5):421-423. doi:10.2350/15-10-1726-CR.1

3. Faye-Petersen OM, Ernst LM. Maternal Floor Infarction and Massive Perivillous Fibrin Deposition. *Surg Pathol Clin*. 2013;6(1):101-114. doi:10.1016/j.path.2012.10.002

4. Bane AL, Gillan JE. Massive perivillous fibrinoid causing recurrent placental failure.*BJOG Int J Obstet Gynaecol*. 2003;110(3):292-295.

5. Taweevisit M, Thawornwong N, Thorner PS. Massive Perivillous Fibrin Deposition Associated With Placental Syphilis: A Case Report. *Pediatr Dev Pathol*. 2021;24(1):43-46. doi:10.1177/1093526620957523

6. Yu W, Tellier R, Wright JR. Coxsackie Virus A16 Infection of Placenta with Massive Perivillous Fibrin Deposition Leading to Intrauterine Fetal Demise at 36 Weeks Gestation. *Pediatr Dev Pathol Off J Soc Pediatr Pathol Paediatr Pathol Soc*. 2015;18(4):331-334. doi:10.2350/15-01-1603-CR.1

7. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol*. 2014;10(8):466-480. doi:10.1038/nrneph.2014.102

8. Burton GJ, Jauniaux E. Placental Oxidative Stress: From Miscarriage to Preeclampsia. *J Soc Gynecol Investig.* 2004;11(6):342-352. doi:10.1016/j.jsgi.2004.03.003

9. Kim EN, Lee JY, Shim JY, et al. Clinicopathological characteristics of miscarriages featuring placental massive perivillous fibrin deposition.*Placenta.* 2019;86:45-51. doi:10.1016/j.placenta.2019.07.006

10. Boog G, Le Vaillant C, Alnoukari F, Jossic F, Barrier J, Muller JY. [Combining corticosteroid and aspirin for the prevention of recurrent villitis or intervillositis of unknown etiology]. *J Gynecol Obstet Biol Reprod (Paris).* 2006;35(4):396-404. doi:10.1016/s0368-2315(06)76411-0

11. Chaiworapongsa T, Romero R, Korzeniewski SJ, et al. Pravastatin to prevent recurrent fetal death in massive perivillous fibrin deposition of the placenta (MPFD).*J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet.* 2016;29(6):855-862. doi:10.3109/14767058.2015.1022864

Acknowledgements: Ms. Mari Kiedysz, MS, PA (ASCP)^{CM} and Dina Hassan, MD for gross and microscopic pathology assistance.

Disclosure of Interests: The authors have no disclosures.

Contribution to authorship: Baillie Bronner worked on literature review, writing the case, and getting patient consent. Margaret Schermerhorn assisted in literature review and drafting of the case. Samantha de los Reyes worked assisted with literature review, case writing, and mentorship. Drs. Anna McCormick and Juliana Sung reviewed, provided commentary and assistance with writing the case.

Detail of Ethics Approval: No IRB was required for case report, however a signed consent was obtained from the patient.

Figure legend

A: fibrinoid deposits surrounding villi; B. Cross section placenta, 34 0/7 weeks: Maturing third trimester placenta with infarct, increased intervillous fibrin, intervillous thrombus and calcifications; C. Fetal Surface; D. Maternal surface with yellow-pink rubbery tissue.