Successful management of acquired hemophilia A, onset during Pregnancy: a case report

Akane Nishi[1], Ayako Muramatsu[2], Eiko Maeda[1], Tsutomu Kobayashi[2], Miyoko Waratani[1] and Jo Kitawaki[1 1]

[1]Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan
[2]Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

Faculty Reporter: Lorella Battini MD, PhD

Dept. of Obstetrics and Gynecology II AOUP (Director: Dr P. Bottone)

OGASH-IAMSS

Hospital Meeting on Acquired Hemofilia A
«Lidio Baschieri» Hall-Cisanello, Pisa, Italy, 14/09/2021
President: Prof. Nadia Cecconi, Hematology Dept., AOUP

- The Authors report the case of a patient with pregnancy-related AHA, in which a successful delivery was achieved

after providing

- immunosuppressive
- prophylactic hemostatic therapies

THE JOURNAL OF
Obstetrics and Gynaecology Research
doi:10.1111/jog.14938
J. Obstet. Gynaecol. Res. 2021

Overview of Acquired Hemophilia A

INCIDENCE : 1,5 individuals/million/years
MORTALITY RATE: 9,1-16%

Definition of AHA[a]

- Characterized by neutralizing autoantibodies (inhibitors) against FVIII

AHA is a rare disease, with 2 peaks in incidence[b]

- One associated with pregnancy (**2-21% of Cases**)
- Another associated with older age

European guidelines published in *Haematologica* in 2020[c]
US guidelines published in the *American Journal of Hematology* in 2017[b]

Because of its rarity, the optimal management for pregnancy-related AHA has not yet been established

a. Tiede A, et al. *Haemophilia*. 2021;27 (suppl 3):5-13; b. Kruse-Jarres R, et al. *Am J Hematol*. 2017;92:695-705; c. Tiede A, et al. *Haematologica*. 2020;105:1791-1801.

CASE REPORT

A 32-year-old primigravida Japanese female at 18 weeks of gestation was admitted at Department of Obstetrics and Gynecology, (Kyoto Prefectural University of Medicine Obstetrics Hospital) with complaints of severe hyperemesis gravidarum.

On physical examination:

- ✓ Extensive ecchymoses occurred in her right thigh and left upper arm
- ✓ Macrohematuria

❖ The Authors obtained written informed consent from the patient, for publication of this case report.

LABORATORY DATA On Admission

Immuno-serological findings		
IgG	754	mg/dL
IgM	106	mg/dL
Anti-β2-GP-I Abs	≤1.2	U/mL
aCL	≤8	U/mL
Lupus AC	Negative	
Biochemistry		
AST	104	IU/L
ALT	173	IU/L
LDH	504	IU/L
ALP	246	IU/dL
γ-GT	34	IU/L
T-Bil	2.91	mg/dL
D-Bil	0.44	mg/dL
Total protein	5.6	g/dL
Albumin	3.2	g/dL
UN	5.1	mg/dL
Cre	0.30	mg/dL
Na	139	mmol/L
K	3.3	mmol/L
Cl	104	mmol/L
Ca	8.3	mg/dL
CRP	0.85	mg/dL

LABORATORY DATA On Admission

Table 1 Laboratory data of the present case on admission

Complete blood count		
WBC	9.1	10^9/L
RBC	3.67	10^{12}/L
Hb	120	g/L
Hct	33.4	%
PLT	242	10^9/L
Coagulation test		
PT	12.1	%
PT-INR	1.02	
APTT	61.5	s
Fibrinogen	549	mg/dL
D-dimer	3.7	mg/mL
Coagulation factor assay		
FVIII activity	1.8	%
FVIII inhibitor	2.3	BU/mL
vWF	164	%

Clinical Course

- **Due to weight loss of 10 kg, intravenous caloric intake was progressively increased**
- **to avoid refeeding syndrome development**
- **Her oral intake gradually increased, and her liver function normalized after 2 weeks**

An APTT cross-mixing test showed an upwardly convex curve after 2-h incubation, indicating the presence of an inhibitor.

The FVIII activity was 1.8%, and the FVIII inhibitor titer was 2.3 BU/mL.

The patient had no personal or family history of abnormal bleeding and no clinical or laboratory indications of autoimmune diseases.

Based on these findings, diagnosis was done of pregnancy-associated AHA

Pregnancy Treatment

- The patient was **initially treated with prednisolone(PSL), 1 mg/kg orally per day**, (50 mg/day) at 20 weeks of gestation to eliminate the inhibitor

- After 5 weeks under Prednisolone , her FVIII inhibitor titer increased to 21.8 BU/mL, and the FVIII activity was <1%; as a result, the APTT was prolonged for over 100 s

- **The second-line treatment, 5 mg/kg/day cyclosporin A (CsA)** administration, was added at 6 weeks after the treatment initiation. **Prednisolone was tapered to 20 mg/day after CsA administration**. Although the FVIII inhibitor titer gradually decreased, FVIII activity remained <10%, and the APTT was approximately 60 s.

- **No complications or adverse drug effects** were providentially associated with pregnancy during treatment of AHA**.**
- **A cesarean section was scheduled for 37 weeks** to reduce the risk of heavy postpartum bleeding and minimize neonatal risks.

SUCCESSFUL DELIVERY

Although complete remission could not be induced in the peripartum period, she gave birth safely by emergency cesarean delivery at 36 weeks, due to onset of labor and not reassuring fetal status

In combination with prophylactic bypass hemostatic therapy

Delivery Management

The Patient was treated with recombinant activated FVII (rFVIIa), 90mg/kg iv every 2-3 h for prophylactic bypassing therapy to prevent perioperative bleeding complications

CS was performed under general anesthesia, without complications during operation

Operative blood loss was estimated about 2118 gr . Two concentrated red blood cells units were transfused and furtherly, two fresh frozen plasma units

NEONATAL OUTCOME

- A Male Baby , wheighed 3302 (+2,2 SD) was born
- APGAR of 5 at 1 and 5 min, respectively .
- Continuous positive airway pressure (C-PAP) was needed and transferral to the NICU.
- No major issue were experienced, but prolonged APTT of 70,8 sec and decreased F VIII activity of 11,5%
- F VIII inhibitor was detected (0,9 BU) in Neonate plasma , indicating transplacental passing. FVIII Inhibitor disappeared on day 8, without bleeding complications

Postpartum Clinical Course

The bypassing agent, rFVIIa, was tapered and discontinued on puerperium day 8 after the postpartum bleeding stopped. The FVIII inhibitor titer decreased to 1.9 BU/mL, and FVIII activity increased to 16.0% after delivery.

At 9 days after delivery, the patient experienced **spontaneous heavy uterine bleeding**. The bleeding was stopped after the application of:

- **direct pressure**
- **administration of tranexamic acid**
- **readministration of rFVIIa**

After 10 days, persistent **and intractable uterine bleeding recurred after discontinuation of rFVIIa**. The coagulation test showed a **slightly prolonged APTT of 44.7 s**

Transvaginal ultrasound : pulsatile blood flow; **Pelvis enhanced computed tomography of the pelvis: extravasation from the uterine artery**, compatible with a **uterine artery pseudoaneurysm (UAP)**

Uterine artery embolization in combination **with bypass therapy** was performed, resulting in **complete hemostasis**

Pt's FVIII inhibitor titer gradually < to 1.1 BU/mL, FVIII activity > to 27.9%, and APTT normalized (36.6 s). **Discharge** on **53rd day after delivery**. **At 60 days after delivery**, the FVIII inhibitor had disappeared, and the **FVIII activity and APTT had normalized**. **OutPt FU : no recurrence**

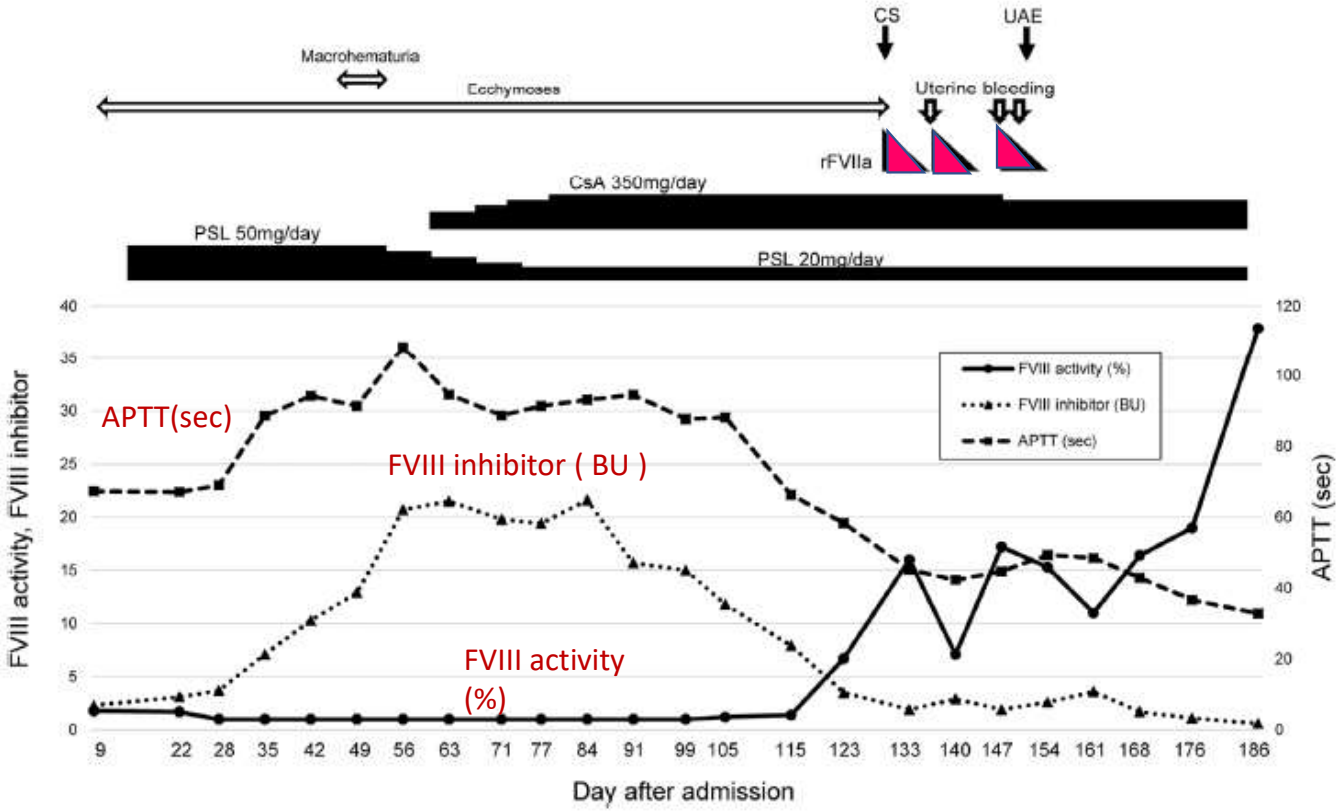

Figure 1 Clinical course of the patient. CsA, cyclosporin A; CS, cesarean section; PSL, prednisolone; rFVIIa, recombinant activated factor VII; UAE, uterine artery embolization

Clinical Course of the Patient

DISCUSSION

Pregnancy-related AHA is rare: 2-21% of cases*
In an observational study in the United Kingdom, only 3 cases of patients in a 2-year period were reported (1:350 000 births)

In this Case Report AHA was **diagnosed**
due to :

- Elevated activated partial thromboplastin time
- Decreased factor VIII activity
- Occurrence of a factor VIII inhibitor

* To the best of our knowledge, antenatally diagnosed AHA is extremely rare because pregnancy-related AHA has mostly been diagnosed after delivery due to massive postpartum bleeding (1-4 months postpartum)

Table 2 Cases of AHA diagnosed during pregnancy

Case no	Author, year (reference)	Age (years)	Parity	Hemorrhagic signs in pregnancy	Week of onset	Factor FVIII		Hemostatic treatment	Immunosuppressive treatment	Mode of delivery	Postpartum bleeding symptoms	FVIII in neonate	Change in inhibitor (period)
						Initial activity levels (%)	Inhibitor titers (BU/mL)						
1[a]	Frick, 1953[9]	25	2	Gross hematuria, extensive subcutaneous hemorrhages	38 weeks	NA	NA	NA	ACTH	Spontaneous vaginal delivery	Vaginal bleeding	NA	NA
2[a]	Marengo-Rowe et al.[10]	14	1	Right flank pain, gross hematuria	29 weeks	3	Detected	Factor VIII	PSL 40 mg daily	Elective low forceps	Vaginal bleeding from mucosal abrasions, excessive bruise	80%	CR (within 1 year)
3[a]	Voke and Letsky[11]	33	1	Spontaneous bruises	First trimester	Undetectable→normal range	Detected→ disappeared	Nothing	Nothing	Spontaneous vaginal delivery	Nothing	37 IU/dL	Spontaneous remission during pregnancy
4	Sultan et al.[12]	29	NA	Multiple ecchymoses, hematuria	22 weeks	NA	300	APCC	IVIG	CS	NA	NA	NA
5[a]	Vincente et al.[13]	29	2	Nothing	11 weeks	NA	175	Nothing	Nothing	Vaginal	Nothing	Normal	NA
6	Solymoss,[14]	34	NA	NA	NA	6	14.4	NA	PSL	NA	NA	NA	CR (2 months)
7	Huang et al.[15] and Solymoss[14]	35	5	Abdominal pain, uterine intrafibroid bleeding, hemarthrosis	Third trimester	2.8	885	APCC	IVIG, CVP chemotherapy → PSL/CPA	NA	NA	NA	CR (176 weeks)
8[a]	Chaari et al.[16]	31	0	Spontaneous bruises of the legs	39 weeks	18	2.3	rFVIIa	PSL, rituximab	Induction, vaginal delivery	Vaginal bleeding	NA	No remission (3.5 months of follow-up)
9	Tengborn et al.[4]	30	NA	Skin + mucosa	90 days before delivery	<1	32	NA	NA	NA	NA	No bleeding symptoms	NA
10[a]	Our case	31	0	Extensive ecchymoses, hematuria	18 weeks	<1	21.6	rFVIIa	PSL, CsA	Emergent CS	Uterine bleeding	17.2%	CR (60 days after delivery)

Abbreviations: APCC, activated prothrombin complex concentrate; CPA, cyclophosphamide; CR, complete remission; CS, cesarean section; CVP, cyclophosphamide, vincristine, and prednisolone; CsA, cyclosporin A; FVIII, coagulation factor VIII; IVIG, intravenous immunoglobulin; NA, not available; PSL, prednisolone; rFVIIa, recombinant activated factor VII. and [a]Full case report.

First Issue to Address

How to Treat the Patient with AHA during Pregnancy ?

High Remission Rate : due to spontaneous disappearance of anti F VIII Inhibitors with Overall Satisfactory Prognosis
Therefore Medical Intervention is not always necessary

Fatal Bleeding Episodes have been reported in several cases of pAHA

Patient Treatment

Immediate administration of Immunosuppressive therapy, to prevent hemorrages during pregnancy and delivery, was started

- In This Case, Standard Prednisolone did not improve the coagulation system of the Patient
- CsA , which is considered safe during pregnancy, successfully reduced the F VIII Inhibitors and restored the F VIII Levels in the Patient

Second Critical Issue to Address: The Bleeding Control during and after Delivery

- **rF VIIa was elected** due to its short half-life, for prophylactic bypass hemostasis therapy to avoid hypercoagulation

- In this **Case Caesarian Section** was considered more safe than vaginal delivery due to the more easy and safe possibility to stop the bleeding point surgically , but further studies are warranted to state the more safe delivery procedure

MANAGEMENT STRATEGY for AHA DIAGNOSED DURING PREGNANCY

Table 3 Proposed management for AHA diagnosed during pregnancy

Anteparatum	Periparatum[f]	Postparatum
Inhibitor eradication[a]	Mode of delivery	Inhibitor eradication[a]
First-line (4–6 weeks)	FVIII inhibitor (−):	Cyclophosphamide or rituximab[c]
Prednisolone 1 mg/kg/day alone or in combination	Vaginal delivery	
with Cyclophosphamide 1–2 mg/kg/day[b]	FVIII inhibitor (+):	
Second-line[c]	Depending on the case[g]	
Cyclosporine[d]		
Tacrolimus[d]		
Azathioprine		
Severe bleeds	Severe bleeds	
Bypass hemostasis[e]	FVIII inhibitor (+): Bypass hemostasis[e]	
	Uterine constrictor	
	Surgical hemostasis for surgical bleeding	
	Manage for obstetric critical hemorrhage	
	Interventional radiology or hysterectomy where necessary	

CONCLUSION

- Accurate and Rapid Diagnosis is required to promote appropriate treatment and avoid life-threatening bleeding
- Consider the Diagnosis of AHA in Cases of Prolonged APTT !
- Multidisciplinary Collaboration among Obstetricians/Gynaecologists , Hematologists, Neonatologists , Anaesthesiologists is Essential for the Management of this Disease

We Would Like to Acknowledge Prof. Akane Nishi and Co-Authors for Publication and Share of this Signficant Case Report with the International Scientific Community, Spreading Worldwide Culture and Practice for this Rare and Life Threatening Complication of Pregnancy.

Great Utility has come both for Students Knowledge and for Obstetric Management

Lorella Battini

Thank You for Your Attention