Coagulación intravascular diseminada

- Sangrado que amenaza la vida se ve en algunas complicaciones del embarazo que producen CID
- Se considera como resultado del desprendimiento de placenta, retención de un feto muerto y embolismo de líquido amniótico.
- Embolismo de líquido amniótico es seguido por colapso vascular materno con disnea, hipotensión y arritmia cardíaca seguido por CID que se manifiesta por sangrado en todo el cuerpo.

Coagulación Intravascular Diseminada

- Hay sangrado en las líneas intravenosas, hematuria, hemoptisis y excesivo sangrado uterino.
- Existen presentaciones atípicas caracterizados por un rápido deterioro del feto seguido por falla respiratoria en la madre y deterioro cardiovascular en el post parto con el desarrollo de CID.
- Se presenta por las propiedades procoagulantes del líquido amniótico que contiene vermix, caseum y células epiteliales escamosas fetales que van a la circulación pulmonar seguido de una respuesta fibrinolítica.

Coagulación Intravascular Diseminada

1. El desprendimiento de placenta produce CID y el espectro de complicaciones al parecer tiene relación a la cantidad de placenta desprendida.
2. Las células trofoblásticas tienen distintas propiedades que activan la coagulación que incluyen la expresión del factor tisular, supresión de la fibrinolisis y la exposición de fosfolípidos aniónicos.
3. Muerte fetal intrauterina produce CID por sustancias tromboplásticas liberado del tejido fetal muerto en la circulación materna. CID evidente se presenta en el 50% de mujeres que retienen un feto muerto por 5 semanas o más.

Enfermedad de von Willebrand

Enfermedad de von Willebrand

- Patrón autosómico dominante
- Desproporción en cuanto la afectación hemorrágica en las mujeres especialmente menorragia y hemorragia post parto.
- En los tipos 1 y 2 los niveles del factor VIII y el FVW aumentan durante el embarazo siendo mayor en el tercer trimestre.
- El riesgo de sangrado en el post parto es significativo (13-29%) ya que cae los valores rápidamente después del nacimiento.

Enfermedad de von Willebrand

- Por tanto en pacientes con EvW tipo1 los niveles de factor VIII deben ser medidos no solamente en la etapa tardía del tercer trimestre también 1 ó 2 semanas en el post parto.
- También debe evaluarse al mes por sangrado.
- Riesgo de sangrado es mínimo cuando los niveles de FVIII son mayores a 40 U/dL.
- Hay reportes de severa trombocitopenia de desarrollo tardío del embarazo en pacientes con EVW tipo IIb
- Reportes de embolia pulmonar después de la administración de concentrados de factor.

Enfermedad de von Willebrand

- A pesar del riesgo de trombosis estos pacientes pueden requerir la transfusión de concentrados de FVW derivado de plasma al momento del parto.
- EVW tipo3 típicamente deben recibir de 40 a 80 UI/kg al día por una semana luego ir disminuyendo la dosis en las siguientes semanas.
- Uso de desmopresina (DDAVP) antes del parto es controversial por el riesgo de vasoconstricción e insuficiencia placentaria y el riesgo de hiponatremia materna.

Table 1 Frequency of postpartum hemorrhage in women with von Willebrand disease

Haemorrhage type	% of all deliveries	% women with VWD	Reference
Primary*	16–29	23–43	
Secondary†	20–29	29–43	[4, 13, 14, 18]
Overall‡	38–50	34–71	
VWD Subtype§			
Type 1	10–37	16–42	[14, 22, 23, 31]
Type 2	50–54	18–83	[14, 22, 31]
Type 3	27	15–26	[22, 31, 33]

*More than 500 ml blood loss within first 24 h after delivery; †more than expected amount of blood loss more than 24 h after delivery until 6 weeks postpartum; ‡overall frequency of postpartum hemorrhage (primary or secondary); §frequency of postpartum hemorrhage in different subtypes of von Willebrand disease.

Table 1. Prospective studies reporting pregnancies using desmopressin for treatment of bleeding disorders.

References	Pregnancies using DDAVP/total pregnancies (*n*)	Bleeding disorder	Indication for DDAVP	Treatment/ dose	Mode of delivery	Maternal outcome	Neonatal outcome
Bjoring *et al.* [7]	7/19	VWD	Second stage of labour – bleeding prophylaxis	Desmopressin 0.3 mg kg^{-1} i.v. Oxytocin 20 U i.v.	NS	PPH in one patient after desmopressin prophylaxis. no side effects reported	No adverse foetal effects
Gojnic *et al.* [11]	32/32	VWD	Bleeding prophylaxis – 36 weeks gestation until 4 weeks postpartum	Desmopressin 300 µg i.n. Cryoprecipitate FFP Hemate P (VIII concentrate)	NVD × 26 LSCS × 6	No abnormal bleeding, no side effects reported	No adverse foetal effects
Mannucci *et al.* [8]	32/32	VWD × 5 haemophilia A carrier × 27	CVS × 20 amniocentesis × 12	Desmopressin 0.3 µg kg^{-1} i.v.	NS	No abnormal bleeding, Mild facial flushing and headache	20 healthy live births 12 elective TOP
Castaman *et al.* [12]	5/6	VWD	Delivery – bleeding prophylaxis	Desmopressin 0.3 µg kg^{-1} i.v. immediately after delivery and 24 h postpartum	NVD × 5 with desmopressin, LSCS × 1 without desmopressin	No abnormal bleeding, no side effects reported	NS
Chediak *et al.* [10]	2/8	VWD	Patient 1 – postpartum bleeding prophylaxis Patient 2 – test dose	Patient 1 – Cryoprecipitate i.v. desmopressin 0.3 µg kg^{-1} × 3 doses Patient 2 – Desmopressin 0.4 µg kg^{-1} i.v.	Patient 1 – LSCS Patient 2 – NS	Patient 1 – hyponatraemia and water intoxication seizure Patient 2 – premature abour	NS
Schulman *et al.* [13]	1/1	Functional platelet disorder	Bleeding prophylaxis post delivery	Desmopressin 0.2 µg kg^{-1} i.v.	NS	Improved bleeding indicies, no side effects reported in pregnant patient	NS

Table 1. Prospective studies reporting pregnancies using desmopressin for treatment of bleeding disorders.

References	Pregnancies using DDAVP/total pregnancies (*n*)	Bleeding disorder	Indication for DDAVP	Treatment/ dose	Mode of delivery	Maternal outcome	Neonatal outcome
Castaman *et al.* [14]	31/31	VWD	Bleeding prophylaxis – Desmopressin given immediately after delivery	Desmopressin 0.3 μg kg^{-1} i.v.	NVD × 31	No abnormal bleeding, no side effects reported	NS
Conti *et al.* [9]	1/5	VWD	Secondary PPH treatment for one patient following NVD	Four unit red cell Tx, desmopressin 0.4 μg kg^{-1} i.v. Methylergonovine	NVD × 2 LSCS × 3	Bleeding stopped post desmopressin and Tx. No side effects reported	NS

NVD, normal vaginal delivery; LSCS, lower segment Caesarean section; TOP, termination of pregnancy; NS, not specified CVS, chorionic villus sampling; PPH, post partum; i.v., intravenous; i.n., intranasal; Tx, transfusion; VWD, von Willebrand disease; BSS, Bernard–Soulier syndrome; EDS, Ehlers–Danlos syndrome; HPS –Hermansky–Pudlak syndrome; SROM, spontaneous rupture of membranes; FFP, fresh frozen plasma.

Table 2. Retrospective studies reporting pregnancies using desmopressin for treatment of bleeding disorders.

References	Pregnancies using DDAVP/ total pregnancies (*n*)	Bleeding disorder	Indication for DDAVP	Treatment/ dose	Mode of delivery	Maternal outcome	Neonatal outcome
Sanchez-Luceros [15]	75/75	VWD	Retroplacental haematoma × 1, prior to cervical cerclage × 4, prior to delivery × 75	Desmopressin 0.3 μg kg^{-1} i.v.	NVD × 30 LSCS × 45	Haematoma resolution. No abnormal bleeding during delivery or postpartum, no side effects reported. No hyponatraemia or thrombotic events	No neonatal bleeding events, no prematurity. Mean birth weight 3.3 kg (range 2.2–4.5 kg)
Ramsahoye *et al.* [19]	1/24	VWD	Bleeding prophylaxis, Desmopressin given immediately after delivery	Desmopressin 0.4 μg kg^{-1} i.v. at delivery, and at 24 and 82 h post delivery	LSCS	No abnormal bleeding for patient given desmopressin prophylaxis no side effects reported	NS
Kadir *et al.* [17]	4/82	Haemophilia A carrier	Bleeding prophylaxis postpartum × 3, Treatment of primary PPH × 1	Desmopressin 0.3 μg kg^{-1} i.v.	NS × 3 NVD × 1	No abnormal bleeding in three patients given prophylactic treatment, No side effects reported.	NS
Ito *et al.* [18]	1/14	VWD	Termination of pregnancy, bleeding prophylaxis	Desmopressin dose not specified	N/A	No abnormal bleeding, no side effects reported	N/A
Kadir *et al.* [16]	1/112	VWD FXI deficiency	Treatment of primary PPH in VWD patient	Desmopressin dose not specified	NVD	No side effects reported	NS
Castaman *et al.* [20]	3/6	VWD	Bleeding prophylaxis post delivery	Desmopressin (i.v.) dose not specified	NVD × 3	No abnormal bleeding, no side effects reported	NS

NVD, normal vaginal delivery; LSCS, lower segment Caesarean section; TOP, termination of pregnancy; NS, not specified CVS, chorionic villus sampling; PPH, post partum; i.v., intravenous; i.n., intranasal; Tx, transfusion; VWD, von Willebrand's disease ; BSS, Bernard–Soulier syndrome; EDS, Ehlers–Danlos syndrome; HPS, Hermansky–Pudlak syndrome; SROM, spontaneous rupture of membranes; FFP, fresh frozen plasma.

Deficiencia de Factores de Coagulación

Deficiencia de Factores de Coagulación

- Portadoras de Hemofilia A y B generalmente tienen niveles de factor del 50% de lo normal, sin embargo, existe un amplio rango de valores reportados al parecer como resultado de la inactivación al azar del cromosoma X.
- Se debe medir la cantidad de factor al inicio del embarazo (primer control) y en el tercer trimestre.
- Hay que tener en cuenta que el Factor IX NO se incrementa durante el curso del embarazo.

Deficiencia de Factores de Coagulación

- Debe determinarse el sexo del bebé para guiar al obstetra durante el parto.
- Hemorragia intracraneal es el sitio más común de sangrado en recién nacidos con hemofilia severa y el mayor potencial de secuelas a largo plazo.
- Factores de riesgo para hemorragia intracraneal incluyen: parto prolongado y uso de instrumental durante el parto.
- Para proteger al feto hemofílico potencial o conocido debe evitarse la extracción al vacío y el forceps usarlo con mucha cautela.

Table 1. Haemostatic levels for invasive procedures during pregnancy and for delivery.

Inherited bleeding disorder	Clotting factor	Haemostatic levels suggested (IU dL^{-1})*	Normal range (non-pregnant) (IU dL^{-1})	Comments
VWD	VWF	50	50–175	
Carrier of haemophilia A	FVIII	50	50–150	
Carrier of haemophilia B	FIX	50	50–150	
Fibrinogen deficiency	Fibrinogen	1.0–1.5†	1.5–4.0	To maintain >1.0 g L^{-1} during pregnancy
FII deficiency	FII	20–30	50–150	
FV deficiency	FV	15–25	50–150	
FVII deficiency	FVII	10–20	50–150	
FX deficiency	FX	10–20	50–150	
FXI deficiency	FXI	20–70	70–150	
FXIII deficiency	FXIII	20–30	70–150	To maintain >3 IU dL^{-1} during pregnancy

*For general guidance only, personal and family bleeding history must be taken into consideration when deciding the need for prophylaxis.
†g L^{-1}.
With permission from Huq *et al.*, [32], *Haemophilia*.

Deficiencia de Factores de Coagulación

- Debe evitarse todas las inyecciones intramusculares en el recién nacido hasta que se haya descartado la hemofilia.
- Las pruebas deben ser realizadas del cordón umbilical.
- El nivel de factor de la madre debe medirse a los pocos días del post parto y con el sangrado menstrual para asegurar una hemostasia adecuada.

Deficiencia de Factores de Coagulación

- **Hemofilia adquirida** causado por autoanticuerpos al factor VIII.
- Usualmente aparece de 1 a 4 meses en el post parto, pero emerge durante el embarazo en hasta 14% de las pacientes.
- Generalmente los títulos de anticuerpos en unidades Bethesda son bajos y en la mayoría de veces desaparecen espontáneamente.
- El inhibidor puede recurrir con subsecuentes embarazos.

Review

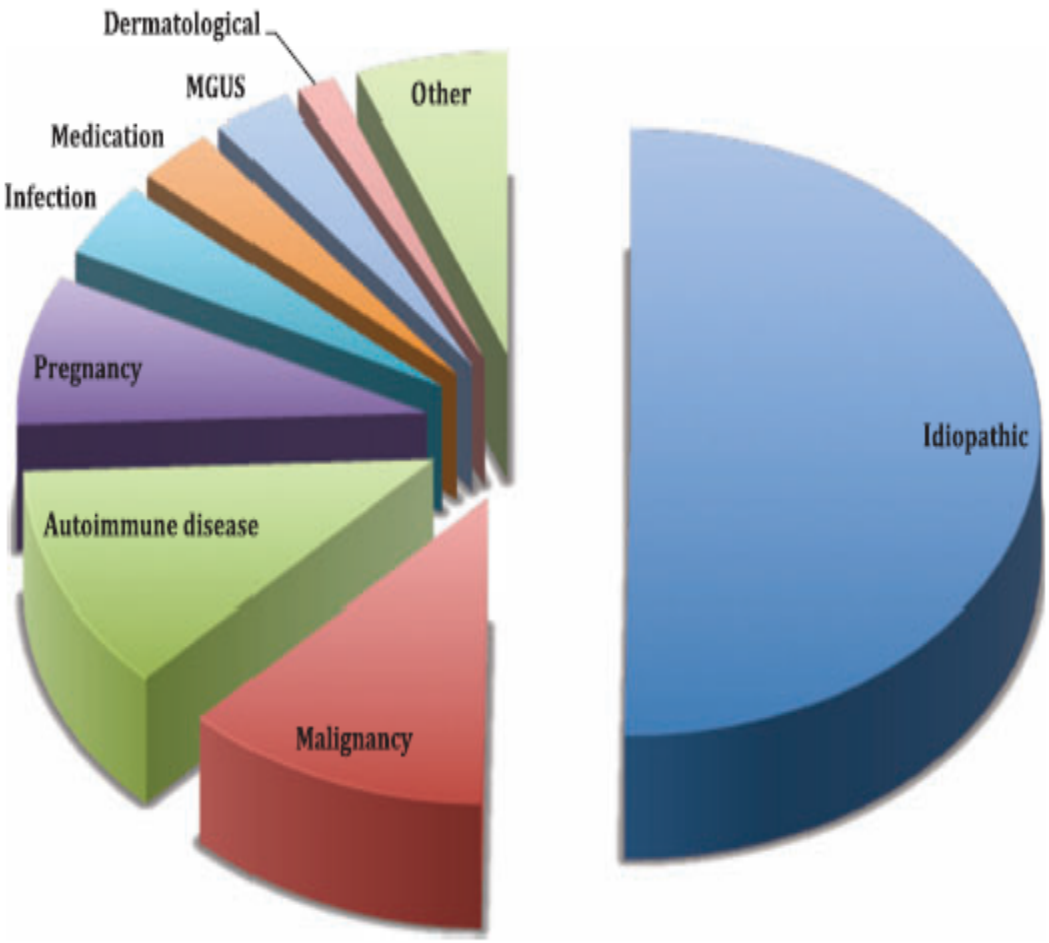
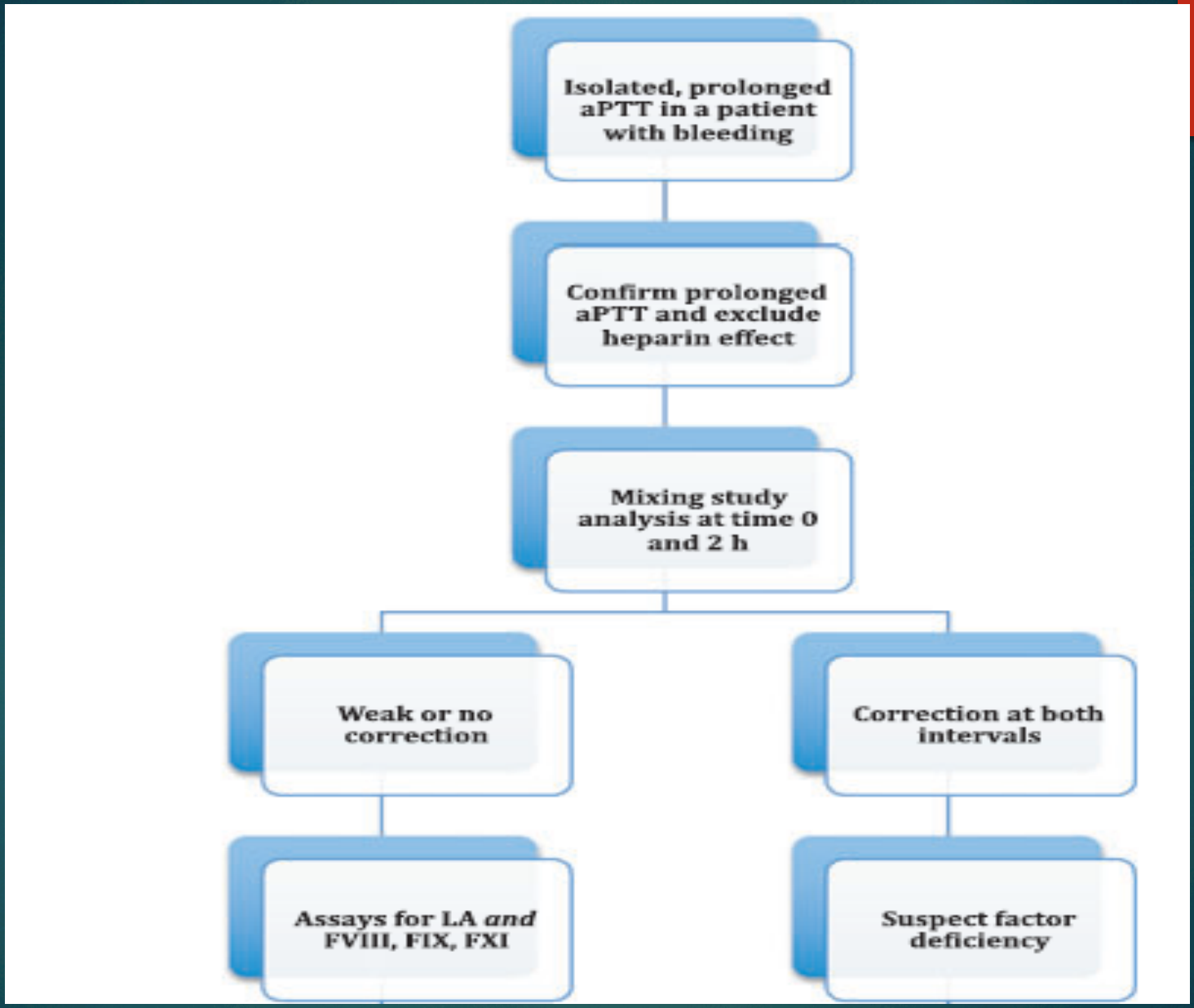


Fig 1. Documented associations with development of factor VIII autoantibodies and acquired haemophilia A, as adopted from data derived from the EACH2 registry (Knoebl *et al*, 2012). MGUS, monoclonal gammopathy of undetermined significance.


Isolated, prolonged aPTT in a patient with bleeding
Confirm prolonged aPTT and exclude heparin effect
Mixing study analysis at time 0 and 2 h
Weak or no correction
Correction at both intervals
Assays for LA *and* FVIII, FIX, FXI
Suspect factor deficiency

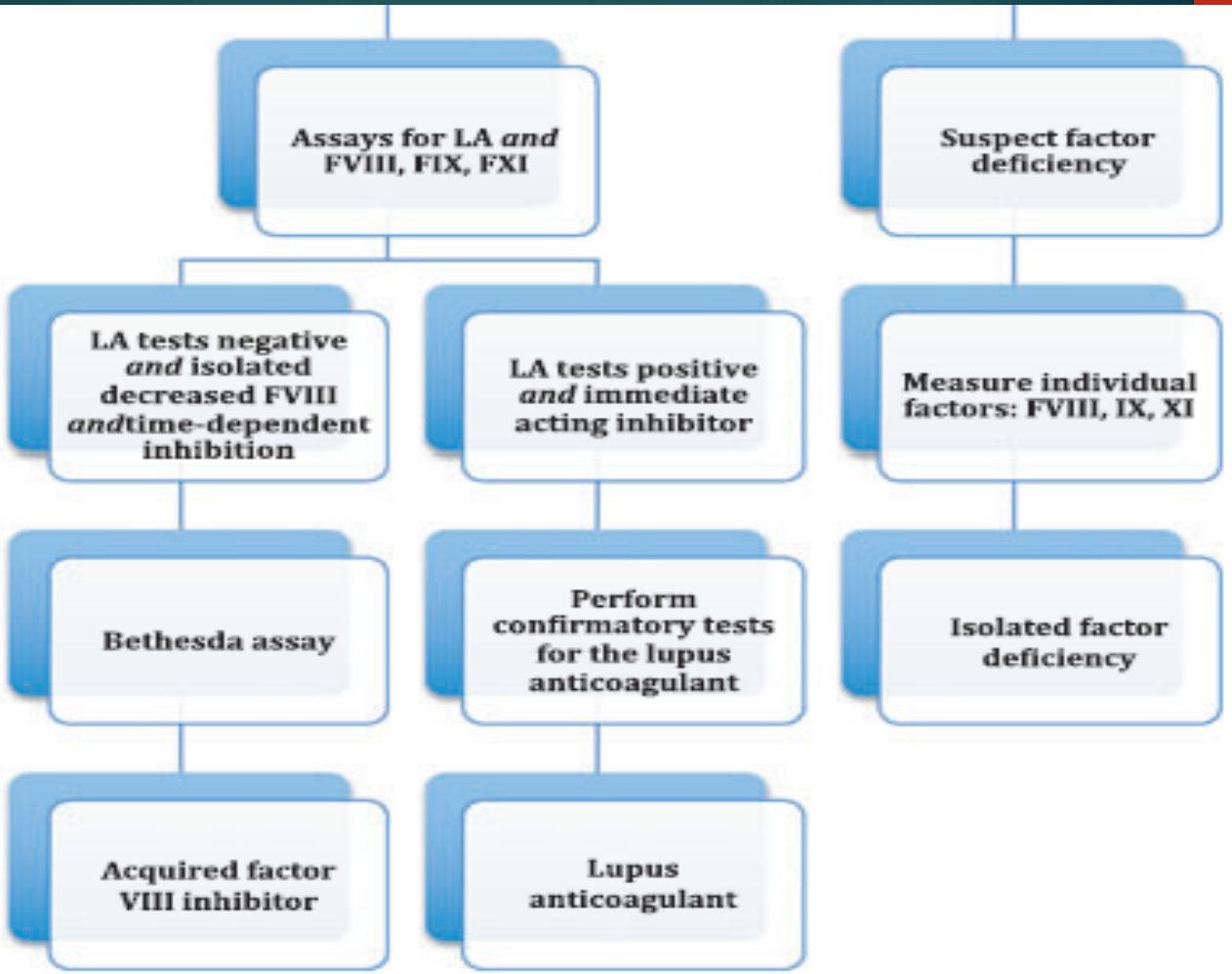


Fig 2. A diagnostic algorithm for the diagnosis of acquired haemophilia A. Patients with an isolated elevation of aPTT should be further evaluated with a mixing study to exclude factor deficiency. Testing to exclude heparin effect and a lupus anticoagulant should also be conducted. Inhibitor titre levels should be obtained with the Bethesda assay. aPTT = activated partial thromboplastin time, AHA = acquired haemophilia A, LA = lupus anticoagulant, FVIII = factor VIII, FIX = factor IX, FXI = factor XI. Adopted from Sborov & Rodgers, 2012 (Sborov & Rodgers, 2012), and reprinted with permission from *Clinical Advances in Hematology & Oncology*.

Table I. Treatment strategies for acquired haemophilia A.

	Bleeding control	Inhibitor eradication
First-line treatment	aPCC or rFVIIa	Steroid ± cyclophosphamide
Second-line strategies	Bypassing agent:	Rituximab ±
	Alternate	Steroid
	Sequential	Cyclophosphamide
	Parallel	Ciclosporin
	Immunoadsorption protocol	Azathioprine
		CVP

rFVIIa, recombinant factor VIIa; aPCC, activated prothrombin complex concentrates; CVP, cyclophosphamide, vincristine, prednisone.

Deficiencia de Factores de Coagulación

- Raramente se identifican gestantes con otras deficiencias que no sean el VIII o IX.
- El más importante es reconocer la deficiencia del Factor XIII que está asociado con abortos hemorrágicos habituales y hemorragia post parto.
- Embarazos que llegan a término que son raros existe complicaciones hemorrágicas como la hemorragia intracraneal en el infante.

Deficiencia de Factores de Coagulación

- El tratamiento es con PFC, crioprecipitado o concentrados de FXIII evita el aborto aunque NO existen estudios controlados.
- La mayoría de autoridades recomiendan terapia profiláctica frecuente durante el embarazo (cada 3 semanas versus cada 5-6 semanas).
- Administrar dosis de pulsos de factor durante el parto o antes de la cesárea para asegurar un nivel de 5% ó más.

Table 2. For the use of regional block in women with inherited bleeding disorders during labour and delivery.

- Multidisciplinary management involving haematologists, anaesthetists, obstetricians and the mother.
- Detailed counselling on the benefits and risks of regional block and its alternatives.
- Informed consent of the patient.
- Careful assessment of coagulation status including assessment of clotting factor during the third trimester and personal and family bleeding history.
- Availability of therapeutic products and adequate response to treatment.
- Plan of management made antenatally, clearly documented and readily available to professionals attending the women in labour.
- Normalization of coagulation defect either because of pregnancy itself or by prophylactic treatment.
- Meticulous technical skills in the administration of regional block by experienced anaesthetist.
- Awareness and surveillance for symptoms and signs of potential complications.

Table 2. Pregnancy outcomes in FXD women *n* (%).

Case reports	15 (100)
Number of pregnancies	24 (100)
Women experiencing successful pregnancy	13 (87)
Women who had more than one successful pregnancy	6 (40)
Live births	21 (88)
Spontaneous abortion	2 (8)
Pregnancy complicated by vaginal bleeding or placental haematoma	3 (14)
Premature labour	10 (48)*†
Neonatal death	4 (19)*
Vaginal delivery	14 (67)*
Caesarean section	7 (33)
Prophylaxis used during pregnancy	4 (21)
Prophylaxis used at delivery	16 (76)*

*Calculated from number of live births.

†Includes maternal and foetal abnormalities not limited to FXD.

FXD, factor X deficiency.

Table 4. Haemostatic therapeutic options for FXD.

Fibrinolytic inhibitors
Aminocaproic acid: 1–3 g orally every 6 h, maximum of 24 g/24 h
Tranexamic acid: 1300 mg orally every 8 h
Fresh frozen plasma (FFP)
10–15 mL kg^{-1}.
Prothrombin complex concentrates (PCCs)
20–40 U kg^{-1} to achieve circulating FX levels of 0.2–0.4 U mL^{-1}
Check FX level 30 min postinfusion to verify level

FX, factor X.

Table 3. Classification of haemostatic drugs used to manage antenatal, peripartum bleeding.

Non-specific (in case of healthy women or mild defects of haemostasis)	Specific (in case of previously diagnosed IBD)
Tranexamic acid (TA) in case of general defects of haemostasis	Desmopressin (DDAVP): mild VWF and FVIII deficiencies or mild platelet defects
Desmo Desmopressin (DDAVP) in case of acquired defects of platelet function (ASA)	VWF/FVIII concentrates: all VWD types unresponsive to DDAVP
	Recombinant FVIII/FIX in symptomatic carriers of haemophilia
	Plasma derived or recombinant concentrates: rare bleeding disorders
	Platelet concentrates: major inherited platelet defects

Table 4. Risk factors and causes of postpartum haemorrhage (PPH)*.

Risk factors	Causes
History of PPH	Uterine atony
Previous caesarean section	Retained placenta
Obesity	Genital tract trauma
Preeclampsia	Coagulation disorders
Placenta praevia	
Placenta abruption	
Fibroids	
Multiple pregnancies	
Macrosomia	
Polyhydramnios	
Chorioamnionitis	
Induced or augmented labour	
Prolonged labour	
Retained placenta	
Operative delivery	

*Not exclusive; data from Stones *et al.* [125] and Sheiner *et al.* [126].

Table 5. Therapeutic options for women with inherited bleeding disorders in pregnancy.

Bleeding disorder	Plasma half-life	Preferred therapeutic option	Other options
Fibrinogen abnormalities	2–4 days	Fibrinogen concentrate	SD plasma
Prothrombin(II) deficiency	2–3 days	PCC	SD plasma
FV deficiency	36 h	SD plasma	SD plasma
FV and FVIII deficiency	–	SD plasma rVIII	FVIII concentrate
FVII deficiency	4–6 h	rFVIIa	FVII concentrate
FX deficiency	40 h	PCC (rFX conc. in clinical trial)	SD plasma
FXI deficiency	52 h	FXI concentrates or Tranexamic acid	SD plasma
FXIII deficiency	11–14 days	FXIII concentrates (rFXIII in clinical trial)	SD plasma
VKCFD	–	Vitamin K	SD plasma PCC

F, factor; r, recombinant; SD plasma, fresh frozen plasma virally inactivated using a solvent detergent technique; PCC, prothrombin complex concentrates; VKCFD, hereditary combined deficiency of the vitamin K-dependent clotting factors.

Muchas gracias!!!