Rare Inherited Bleeding Disorders in Pregnancy – Full Clinical Guideline

Reference No.: Obs/07:23/B1

Contents

1. Introduction and Background

The rare inherited bleeding disorders account for 3-5% of all inherited coagulation deficiencies and include all those factor deficiencies other than Von Willebrand Disease and Haemophilia A or Haemophilia B (refer to separate Trust guidelines for management of these conditions in pregnancy).
They are usually caused by recessive inheritance and so are more common in ethnic groups in which consanguineous partnerships are common because of the higher likelihood of homozygosity. Many heterozygote carriers are asymptomatic.
Pregnancy and childbirth present significant haemorrhagic risks for women with significant bleeding disorders requiring careful management and planning

The evidence for care in pregnancy is weak and recommendations in this guideline are in keeping with current British Society for Haematology/ UKHCDO guidelines on rare coagulation disorders, supported by the RCOG.

For the purposes of this guideline this includes heritable deficiencies of:

- Fibrinogen
- Prothrombin
- Factor V

- Factor V11
- Factor X
- Factor X1
- Factor X111
- Combined Factor V and FV111 deficiency

2. Purpose and Outcomes

To guide all relevant healthcare professionals in the principles of the management of rare inherited bleeding disorders in pregnancy. This does not remove the need for specialist multidisciplinary care by experts in Obstetric Haematology.

3. Abbreviations

APH	-	Antepartum Haemorrhage
C/S	-	Caesarean Section
COH	-	Combined Obstetric Haematology
MDT	-	Multidisciplinary Team
NSAID	-	Nonsteroidal Anti-inflammatory Drug
PPH	-	Postpartum haemorrhage
SD-FFP	-	Solvent Detergent Fresh Frozen Plasma
TXA	-	Tranexamic acid
UKHCDO	-	UK Haemophilia Centre Doctors Organisation

4. Preconception

Offer women with a personal or family history of a rare inherited bleeding disorder, referral to COH for preconception assessment, workup and pregnancy care planning

5. General Principles of Antenatal Care

- Book for Consultant Led Care under the Combined Obstetric Haematology (COH) Clinic
- Women with significant bleeding phenotype, severe rare (homozygous) deficiencies or unknown bleeding risk should be booked for delivery in Derby (Haemophilia Care Centre) as they require MDT management with access to 24 hour blood products, factor replacement and specialist haematological advice
- Individualised MDT care plans will be required for mother and fetus/neonate, taking into account the specific bleeding disorder, bleeding phenotype and specific pregnancy bleeding risks (APH, pregnancy loss, PPH)
- Refer to anaesthetic Antenatal Clinic for planning related to analgesia and anaesthesia
- Optimise maternal Hb, correct Fe deficiency
- Factor levels should be checked at booking, before invasive procedures, if bleeding complications and in third trimester
- Consider need for replacement therapy or TXA if spontaneous miscarriage, TOP, invasive procedure
- ECV contraindicated if severe deficiency.
- Factor replacement usually advised for delivery in severe factor deficiency and/or bleeding history. If available specific recombinant or virally inactivated plasma derived concentrates should be used in preference to FFP or cryoprecipitate
- TXA 1g qds can be used for minor bleeds
- Neonatal care plan and alert to be generated antenatally.

Specific Bleeding Disorders

5.1 Fibrinogen Deficiency

Afibrinogenaemia (autosomal recessive) – severe deficiency
H*ypofibrinogenaemia* (autosomal dominant)- partial quantitative
Dysfibrinogenaemia (autosomal dominant) – partial quantitative +/- qualitative defect

Severe deficiency associated with APH, PPH, poor wound healing and splenic rupture in mum and ICH and umbilical bleeding in neonate

Hypo and dysfibrinogenaemia can in addition be associated with pregnancy loss, arterial and venous thrombosis. Very variable clinical phenotype

Levels may increase in pregnancy

Treatment Options

- Prophylaxis if functional fibrinogen < 0.5g/litre with fibrinogen concentrate 50-100mg/kg twice weekly to maintain trough > 1g/litre
- Additional treatment for delivery to maintain activity > 1.5g/litre for at least 3 days
- TXA for minor bleeding
- Consider need for thromboprophylaxis depending on clinical phenotype, presence of VTE risk factors and genetic subtype as increased risk of thrombosis with fibrinogen concentrate

5.2 Prothrombin deficiency (Factor 11)

Levels do not increase in pregnancy
Reported association with APH, pregnancy loss and PPH

Treatment options

- If already on prophylaxis with prothrombin concentrate continue through pregnancy to maintain trough levels > 0.1 iu/ml (> 10%)
- TXA for minor bleeds
- If Factor 11 activity < 0.2 iu/ml (< 20%) give prothrombin complex concentrate 20-40 iu/kg once in established labour or before caesarean section to achieve levels 0.2-0.4 iu/ml (20 – 40%). Consider further PCC 10–20 iu/kg at 48 h to maintain FII activity >0.2 iu/ml (>20%) for at least 3 d.

5.3 Factor X1 deficiency

Autosomal disorder with both dominant and recessive inheritance patterns, more common in Jewish population
Variable phenotype – Plasma levels correlate poorly with bleeding severity. The bleeding phenotype correlates better with pregnancy related bleeding risk

Heterozygotes (mostly asymptomatic) have mild/moderate reductions in Factor X1 levels.
Homozygotes/compound heterozygotes have levels below 0.15-0.2 iu/ml (15 – 20%) and have an increased bleeding risk after surgery/trauma

Levels do not increase in pregnancy

Increased risk PPH and bleeding after miscarriage, TOP or surgery if bleeding phenotype or severe deficiency

Treatment Options

- TXA (cannot be used with Factor concentrate as increased thrombotic risk)
- Solvent detergent (S-D) FFP
- Factor X1 concentrate (plasma derived, carries increased risk thrombosis and transfusion transmitted infection)

- For delivery in all women with factor XI activity <0.15 iu/ml (15%) in the third trimester, consider FXI concentrate 10–15 iu/kg or SD-FFP 15–25 ml/kg and tranexamic acid 15–20 mg/kg at established labour or before caesarean section
- For delivery in women with FXI activity 0.15–0.7 iu/ml (15 – 70%) in the third trimester and a history of bleeding or no previous haemostatic challenges, consider tranexamic acid 15 mg/kg or 1 g four times a day continued for at least 3 days.
- For delivery in women with FXI activity 0.15–0.7 iu/ml (15 – 70%) in the third trimester and no bleeding despite haemostatic challenges, only consider FXI concentrate or antifibrinolytics if abnormal bleeding occurs

5.4 Severe Factor V11 deficiency

Mild asymptomatic deficiency not uncommon, levels 0.15 – 0.35 iu/ml (15 – 35%)
Weak correlation between Factor levels and bleeding severity.
Bleeding phenotype more predictive than Factor levels.

Severe bleeding more likely if Factor V11 levels less than 0.01 iu/ml (1%)
Association with APH, PPH and pregnancy loss reported if prior bleeding history

Treatment recommended for delivery if Factor V11 < 0.2 iu/ml (< 20%) in third trimester and prior bleeding history OR in response to abnormal bleeding

Treatment options

- TXA only if mild bleeding
- For delivery in women with FVII activity <0.2 iu/ml (20%) in the third trimester, who require caesarean delivery or who have a history of bleeding, consider rFVIIa 15–30 micrograms/kg every 4–6 h for at least 3 days. For all other women with FV11 deficiency, consider rFVIIa 15–30 micrograms/kg only in response to abnormal bleeding

5.5 Factor V deficiency

Associated with PPH
Levels do not increase in pregnancy
Weak correlation between bleeding severity and Factor levels so bleeding phenotype important

Treatment options if bleeding or for delivery

- TXA for minor bleeding
- For delivery in women with FV activity <0.2 iu/ml (20%), consider SD-FFP 15–25 ml/kg once in established labour or before caesarean section, to achieve FV activity 0.2–0.4 iu/ml (20 – 40%. Consider further SD-FFP 10 ml/kg at 12-hr intervals to maintain FV activity >0.2 iu/ml (20%) for at least 3 days

5.6 Severe Factor X deficiency

Associated with APH, PPH and pregnancy loss
Reasonable correlation between Factor levels and bleeding severity
Levels increase in pregnancy

Treatment options

- Antenatal prophylaxis with prothrombin complex concentrate 20-30 iu/kg 2-3 times weekly
- For delivery in women with FX activity <0.3 iu/ml (30%) in the third trimester who have a history of bleeding and all those who require caesarean section, consider PCC 20–40 iu/kg to achieve FX activity >0.4 iu/ml (40%). Consider further PCC 10–20 iu/kg once daily to maintain FX activity >0.3 iu/ml (30%) for at least 3 days

5.7 Severe Factor X111 deficiency

Levels fall in pregnancy
Severe deficiency associated with a high rate of pregnancy loss and bleeding

Treatment options

- Long term prophylaxis with Factor X111 concentrate if personal or family bleeding history
- women with FX111 deficiency on prophylaxis with FXIII concentrate should be monitored closely throughout pregnancy
- Increased intensity of prophylaxis recommended every 14-21 days to maintain FX111 > 0.2 iu/ml (> 20%)
- consider additional FXIII concentrate 10–40 iu/kg once in established labour or before caesarean section, depending on the interval since last prophylaxis

5.8 Combined Factor V and V111 deficiency

Reasonable correlation between Factor levels and bleeding severity
Factor V111 levels rise in pregnancy but not Factor V
Associated with PPH

Treatment options

- For delivery in women with FV activity <0.2 iu/ml (20%) in the third trimester, consider SD-FFP 15–25 ml/kg once in established labour or before caesarean section to achieve FV activity 0.2–0.4 iu/ml (20 – 40%).
- Consider further SDFFP 10 ml/kg once every 12 h to maintain FV activity >0.2 iu/ml (20%) for at least 3 d. Consider additional rFVIII if the FVIII activity is <0.5 iu/ml (50%) in the third trimester

6. <u>Intrapartum Care – refer to individualised MDT Care plan</u>

6.1 General Principles

- FBC, G+S, +/- Factor levels on admission
- Establish iv access
- Senior Midwife to provide intrapartum care
- Senior Obstetrician for obstetric decisions/operative interventions
- Senior anaesthetist if neuraxial analgesia/anaesthesia
- IM analgesia may be contraindicated – see individualised care plan
- Follow individualised care plan for intrapartum management and need for TXA or corrective therapy at onset of labour
- Keep hydrated
- Aim to avoid prolonged labour/complicated delivery
- Active third stage
- Early repair of perineal trauma by senior midwife or obstetrician to reduce risk of blood loss and perineal haematoma formation

6.2 Maternal Bleeding Risk

6.2.1 *High Risk*

Includes severe (homozygous) rare inherited bleeding disorders and fibrinogen deficiency with a bleeding phenotype
Require adequate replacement therapy prior to labour/surgery

- Consider TXA
- Neuraxial Anaesthesia/analgesia only if adequate replacement therapy confirmed and haemostatic defect corrected
- Maintain adequate levels for 3 days after vaginal birth or 5 days after instrumental or C/S

6.2.2 *Medium Bleeding Risk*

Factor X1 deficiency with clinical bleeding phenotype, very low Factor levels or previous PPH

- Adequate replacement therapy at onset of labour
- Avoid Neuraxial anaesthesia/analgesia unless adequate replacement confirmed
- Maintain levels as above

6.2.3 *Unlikely to have a bleeding risk*

Heterozygous inherited bleeding disorder without a bleeding phenotype
Factor V11 Deficiency (any severity)

- No replacement therapy
- Consider need for TXA
- Able to have neuraxial analgesia/anaesthesia
- If unknown bleeding phenotype and Factor X1 deficiency, neuraxial analgesia/anaesthesia on risk/benefit ratio after careful counselling

6.3 Risk to fetus

6.3.1 *Higher risk of bleeding*

Severe homozygous inherited bleeding disorders or severe platelet disorders

- Mode of delivery to take into consideration maternal and fetal factors
- Avoid FBS, FSE, Ventouse, rotational or midcavity forceps

6.32 *Unlikely to be a risk*

Heterozygous rare bleeding disorders

- Normal intrapartum management

7. Postpartum Care

7.1 Mother

- Avoid NSAID if severe deficiency
- IM injections in severe deficiency only if coagulopathy corrected
- Thromboprophylaxis - requires individual assessment of bleeding versus thrombosis risk. If adequate replacement therapy LMWH can be considered, but in severe deficiency may be best to avoid as even after replacement therapy, consistent normalisation of haemostasis may not be guaranteed. Mechanical thromboprophylaxis should be maintained
- Consider need to continue TXA and risk of secondary PPH after discharge. Ensure mother knows to report excessive bleeding and has emergency contact numbers

7.2 Neonate

- Cord sample for Factor assay with severe (homozygous) deficiencies
- Oral Vitamin K unless result known to be normal
- Heel prick test- maintain pressure for 5 minutes
- Diagnosis of deficiency may be possible at birth with Factor V111, V and Fibrinogen although will require confirmatory testing at 3-6 months
- All other deficiencies cannot be diagnosed at birth
- There is a risk of neonatal ICH with severe homozygous, compound heterozygous deficiencies and severe fibrinogen deficiency with a bleeding phenotype. The neonatal team should be alerted to this especially if any significant trauma at delivery

8. Monitoring Compliance and Effectiveness

As per agreed business unit audit forward programme

9. References

1. RCOG/UKHCDO GTG No 71 Management of inherited Bleeding disorders in pregnancy BJOG 2017; 124:e193-e263

2. Mumford et al: Guideline for the diagnosis and management of the rare coagulation disorders. A United kingdom Haemophilia Centre Doctors Organization guideline on behalf of the British Committee for Standards in Haematology: BJH, 2014, **167,** 304-326

Documentation Control

Reference Number: Obs/07:23/B1	**Version: 2**		**Status: FINAL**	
Version / Amendment	Version	Date	Author	Reason
	1	Feb 2019	Miss R Hamilton – Consultant Obstetrician	New
	2	May 2023	Miss R Hamilton – Consultant Obstetrician	Review
Intended Recipients:				
Training and Dissemination: Cascaded through lead sisters/midwives/doctors; Published on Intranet; NHS Mail circulation list.				
To be read in conjunction with:				
Development / review of Guideline:	Miss R Hamilton – Consultant Obstetrician			
Consultation with:	Dr A McKernan – Consultant Haematologist			
Business Unit sign off:	02/05/2023: Maternity Guidelines Group: Miss S Rajendran – Chair 19/06/2023: Maternity Governance Group - Mr R Deveraj			
Notification Overview sent to TIER 3 Divisional Quality Governance Operations & Performance: 20/06/2023				
Implementation date:	05/07/2023			
Review Date:	July 2026			
Key Contact:	Joanna Harrison			