Von Willebrands Disease in Pregnancy – Full Clinical Guideline

Reference No.: UHDB/Obs/07:23/B2

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1. Introduction and Background

Von Willebrands disease (VWD) is the commonest inherited bleeding disorder with variable penetrance and expressivity. It results from either a quantitative or qualitative deficiency of VonWillebrand Factor (VWF), a large glycoprotein essential for thrombus formation: it is a carrier protein for Factor V111 in the circulation and mediates platelet aggregation and adhesion.
The prevalence of clinically relevant VWD is 1 in 10,000 although less symptomatic cases may be more prevalent up to 1 in 1000.

There are three major subtypes:

Type 1 (70-80%)
Partial quantitative deficiency of structurally normal VWF
Mostly autosomal dominant inheritance (either parent can pass it on to a fetus of either sex)
Characterised by variable penetrance and expressivity of the VWD phenotype

Type 2 (20%) Qualitative defects of VWF which cause functional reduction in VWF activity. These are usually inherited in a dominant pattern apart from Type 2N which is recessive inheritance

Type 2A	Decreased platelet adhesion with selective deficiency of high molecular weight (HMW) multimers
Type 2B	Increased platelet binding causing exacerbation of thrombocytopenia
Type 2M	Reduced platelet adhesion without selective deficiency of HMW multimers
Type 2N	Reduced binding affinity for FV111 causing low levels of FV111

Type 3 (very rare)
Virtually complete deficiency of VWF with secondary severe deficiency of Factor V111. These patients usually have a severe bleeding phenotype.
Recessive inheritance – are usually homozygotes or double heterozygotes (frequent consanguinity).

2. Scope

To provide guidance to all health care professionals involved in the care of a woman with VWD who may either be planning a pregnancy or who is pregnant.

3. Abbreviations

C/S	-	Caesarean Section
COCP	-	Combined Oral Contraceptive Pill
COH	-	Combined Obstetric Haematology
DDAVP	-	Desmopressin
ECV	-	External Cephalic Version
ECH	-	Extracranial Haemorrhage
EPR	-	Electronic Patient Record (BadgerNet)
FV111	-	Factor V111
HMW	-	High Molecular Weight
ICH	-	Intracranial Haemorrhage
IUD	-	Intrauterine Device
NSAID	-	Nonsteroidal Anti-inflammatory Drug
PPH	-	Post Partum Haemorrhage
RPOC	-	Retained Products of Conception
Ricof	-	Ristocetin Cofactor Activity
TXA	-	Tranexamic Acid
VBB	-	Vaginal Breech Birth
VWD	-	Von Willebrand Disease
VWF	-	Von willebrand Factor

4. Laboratory Tests used to Monitor VWD in Pregnancy

VWF antigen (VWF: Ag)
Measures concentration of VWF in plasma

VWF Ristocetin Cofactor Activity (VWF: Ricof)
Measures ability of VWF to bind to platelets ie functional activity

Factor V111 (FV111)
Measures amount of circulating FV111

Other tests may have been done at time of diagnosis or for genetic investigation but these would not routinely be required in pregnancy and should only be done on the advice of a Haematologist

Samples required are TWO BLUE TOP (CITRATE) bottles, sent immediately to Lab together with a FBC. Request Bleeding investigations on ICM.

5. Expected Changes in VW levels in Pregnancy

Type 1 Usually a progressive rise in FV111, VWF antigen and VWF function
Start to rise from early first trimester
Most women expected to normalise by third trimester
If baseline VWF function < 0.15 iu/ml (< 15%) less likely to normalise

Type 2 VWF antigen and FV111 often increases
VWF function remains low (increase in abnormal VWF protein).
Defect doesn't correct in Type 2A and 2M VWD

In type 2B often have associated thrombocytopenia
In type 2N may have low FV111

Type 3 FV111 and VWF levels remain low

Postnatal Fall in VWF and FV111 levels to baseline between 24 hrs – 14 days

Neonate Neonatal VWF levels physiologically increased at birth

Due to these physiological changes it is not possible to exclude a diagnosis of VWD in pregnancy. If referred due to a family history, will need to be managed as if has VWD and tested outside of pregnancy. Risk of PPH persists postnatal due to fall in levels.

6. Risks to Mother and Baby

6.1 Mother

Increased risk of

- Antepartum Haemorrhage (APH) increased ten-fold
- Primary PPH 15-30% women
- Secondary PPH 25% women
- Perineal Haematoma increased
- Need for Blood transfusion
- Mortality

No increased risk of miscarriage, preterm birth, abruption, fetal growth restriction or stillbirth.

6.2 Fetus/Neonate

- Physiological increase in levels confers some protection against bleeding
- Type 2/3 and severe Type 1 may have reduced levels at birth with increased risk bleeding, both ECH and ICH
- Risk of life threatening Intracranial Haemorrhage (ICH) extremely rare

7. Preconception

It is recommended that the following women are offered referral to the Combined Obstetric Haematology clinic for preconception work up and counselling:

- Women with VWD
- Women whose partners are known to have VWD
- Women with a family history of VWD, not previously investigated

At preconception assessment:

- Establish bleeding phenotype, historical diagnosis and response to Desmopressin (DDAVP), if not already known
- Establish Baseline FBC, ferritin, coagulation and VW Levels and document molecular analysis/genetics if available. Correct Fe deficiency prior to pregnancy
- Review vaccination status and immunity to Hep A and B
- Discuss likely effect of pregnancy on VW levels and bleeding risk
- Discuss inheritance and option of prenatal diagnosis with Type 3 VWD
- Discuss maternal and neonatal risks and review of other pregnancy risk factors
- MDT Care plan for pregnancy management, delivery and postnatal care and neonatal care
- Consent for administration of plasma derived factor concentrates if likely to be required

8. Antenatal Care

- Book under Consultant Led Care for delivery at Derby site (Haemophilia Care Centre). Refer early for booking under care of Consultant Obstetrician for Obstetric Haematology. Care will subsequently be provided in the joint Obstetric Haematology Clinic (COH).
- Patients with Mild Type 1 VWD who achieve normal levels may be suitable for delivery locally in Burton and managed jointly with Haemophilia Care Centre
- MDT approach to care to include obstetric, haematology, anaesthetic, midwifery and neonatal care plan
- Check VW Levels in early pregnancy in case of early pregnancy bleeding complications
- Repeat if need for invasive procedures eg amniocentesis or admitted with bleeding complications
- Repeat in the third trimester (28, 32-34 weeks).
- Ensure patient is aware of emergency Contact numbers for the Haemophilia Centre through the Clinical Nurse Specialist (CNS) for Haemostasis and Thrombosis and the Pregnancy Assessment Unit (PAU) 24 hour triage telephone number.
- Refer to Anaesthetic Antenatal Clinic for plan for analgesia and anaesthesia
- Neonatal alert to be completed by MDT

Invasive procedures:
Requires FV111 and VWF levels > 0.5 iu/ml (>50%)
If lower will require pre procedure haemostatic support in form of either DDAVP or Factor Concentrate – on advice of Consultant Haematologist

Requires Platelets > 50
If lower will need platelet transfusion – on advice of Consultant Haematologist

TOP/Miscarriage
Requires levels as above

ECV
Contraindicated for fetuses at risk of having Type 2/3 VWD

MDT Labour/Delivery Care Plan

Aim to finalise around 34 weeks depending on subtype and change in levels.
Discuss and agree with the patient and members of the MDT.

A copy of this plan should be made available in the EPR.

9. Treatment Options

The following agents may be required as indicated by the individual care plan

Tranexamic Acid

- Antifibrinolytic
- Can be used as sole therapy if VW levels and FV111 > 0.5 iu/ml (50%)
- Used in combination with DDAVP/Factor concentrates if levels below 0.5iu/ml (50%)
- Oral or iv, dose 1g qds
- Available on LW

Desmopressin (DDAVP)

- A synthetic vasopressin analogue which increases endogenous VWF and FV111 by causing release from endothelial cells.
- Mainly used in Type 1 VWD known to be DDAVP responsive
- Suitable in some Type 2 subtypes. Not recommended for Type 2B due risk thrombocytopenia
- Dose 0.3micrograms/kg booking weight sc or iv
- Takes effect within 30-60 minutes
- Lasts 8-10 hours
- If effective will increase VWF and FV111 3-5 fold
- Increased risk maternal fluid retention and hyponatraemia. Fluid restrict 1 litre/24 hours after use. If additional fluids required monitor electrolytes
- Prolonged use should be avoided
- Safe in pregnancy but contraindicated if PET, uncontrolled hypertension or cardiac disease/failure
- Obtain from Pharmacy
- Take pre and post (30 mins) levels of VWF antigen, function and FV111 and discuss results with Haematologist

VWF concentrate

- Pooled plasma product, virally inactivated, contain FV111 as well as VWF
- Used when DDAVP unsuitable
- Use 1 hour preprocedure or at outset of labour
- Aim to increase VWF and FV111 above 0.5 iu/ml (50%) target peak 1.0 iu/ml (100%)
- Maintain for 3 -5 days depending on mode of delivery or delivery complications
- Available from Haemophilia CNS during working hours, otherwise discuss with on call Haematologist
- Take pre and post (30 mins) levels of VW antigen, function and FV111

Platelets

- Sometimes required for Type 2B VWD
- Discuss with Consultant Haematologist

10. Intrapartum Care

Type 1
Generally will not require prophylactic treatment for delivery provided levels have normalised

Type 2
Prophylactic treatment may be required on an individual basis – see MDT care plan

Type 3
Prophylactic treatment required for all types delivery

Mode of delivery is determined by Obstetric indications.
No contraindication to vaginal birth simply due to VWD.
Vaginal Breech Birth (VBB) not recommended

10.1 General Principles

- Take blood for FBC, clotting, G+S on admission
- Take blood for VW levels if less than 0.5iu/ml (50%) at last check
- Establish iv access
- Senior midwife to provide intrapartum care
- Senior Obstetric decisions and Senior Obstetrician if requires operative intervention
- Senior anaesthetist if having neuraxial analgesia/anaesthesia
- Aim to avoid prolonged labour or need for complicated delivery
- See below for advice re specific intrapartum procedures
- Active third stage
- Early suturing of episiotomy or perineal trauma by experienced midwife or obstetrician
- Inform neonatal team

10.2 Analgesia/ Anaesthesia – refer to individual care plan where present

- Can be offered im injections if FV111 and VW levels > 0.5 iu/ml (> 50%) and platelets > 50
- Neuraxial analgesia/anaesthesia can be offered to majority of Type 1 whose FV111 levels and VWF function are > 0.5 iu/ml, >50%) (or raised to > 0.5 iu/ml by prophylactic treatment)
- Neuraxial analgesia/ anaesthesia generally not recommended for Type 2 VWD as even with replacement therapy and VWF > 0.5 iu/ml (> 50%) haemostasis may not normalise
- Neuraxial analgesia/anaesthesia not recommended for Type 3
- Experienced anaesthetist to carry out
- Consider need to check VW levels and give repeat treatment before removal of epidural catheter as they may fall rapidly after birth.

10.3 Intrapartum Procedures – refer to individual care plan

10.3.1 Fetus/Neonate at high risk of Bleeding

- *Type 3 VWD*
- Consider mode delivery taking into account maternal and fetal factors
- Avoid FBS, FSE, Ventouse
- Avoid Midcavity or rotational forceps

10.3.2 Fetus/Neonate with medium bleeding risk

- *Type 2VWD*
- Avoid Ventouse
- Avoid Midcavity or rotational forceps if possible aiming for least traumatic mode delivery- senior Obstetrician only to perform
- FBS/FSE can be considered judiciously by senior obstetrician

10.3.3 Fetus/Neonate with mild bleeding risk

- *Clinically moderate or severe Type 1 VWD in family*
- Consider avoidance of Ventouse
- Forceps can be used by Senior Obstetrician
- Judicious use of FSE/FBS by senior Obstetrician

10.3.4 Fetus /Neonate unlikely to have bleeding risk

- *Clinically Mild Type 1 VWD in family*
- No special precautions required, normal management

11. Postpartum Care

11.1 Mother

- Observe for primary PPH
- Check VW levels routinely at 24 hours or if bleeding concerns
- Levels need to be maintained > 0.5 iu/ml (>50%) for 3 days following uncomplicated vaginal delivery and 5 days following instrumental delivery or C/S. The need for ongoing monitoring will be determined by the COH team – see individual care plan
- Continue oral TXA postnatal and after discharge – duration to be decided by COH team. Inform mum this is safe for breastfeeding
- Avoid NSAID or im injections if FV111 or VW function less than 0.5 iu/ml (50%)
- Thromboprophylaxis for inpatients to be considered on individual basis depending on correction of VW and FV111 levels and VTE risk factors. If LMWH contraindicated, mechanical thromboprophylaxis should be maintained
- Ensure patient has contact numbers for COH team and CNS Haemostasis after discharge and is aware of risk of secondary PPH and need to report increased bleeding
- COH follow up as per individual care plan – discuss with COH team and ensure patient has appointment time
- Late PPH non responsive to TXA and not due to RPOC or endometritis can be managed by COCP or the Levonorgestrel intrauterine device (IUD)

11.2 Baby

- See individual neonatal care plan in maternal intrapartum care plan
- It is not usually possible to make a formal diagnosis of VWD in the neonatal period as levels will be increased due to the stress of delivery **.** Repeat testing will be required when baby is older
- **Fetus at risk of Type 1 VWD** – no sample required and can have normal neonatal management including im Vitamin K and injections
- **Fetuses at risk of Type 2/3 VWD** require cord sample for VW function, antigen and FV111. Send one blue top citrate sample clearly marked as *NEONATAL CORD SAMPLE FOR VW STATUS* immediately to Haematology Lab and phone to inform them.
- **Fetus at risk of type** 2B **VWD** - require FBC also
- Give Vitamin K orally and avoid im injections unless levels > 0.5 iu/ml (> 50%)
- Heel prick tests- pressure applied for 5 minutes
- **Fetus at risk of Type 3 VWD** consider need for short term prophylaxis and need for routine imaging if any significant trauma at delivery
- Follow up in Paediatric Haematology Clinic after discharge – see maternal Care Plan
- Any bleeding concerns – discuss with Consultant Haematologist Dr McKernan

12. Monitoring Compliance and Effectiveness

As per agreed business unit audit forward programme

13. References

1. RCOG/UKHCDO GTG No 71: Management of Inherited Bleeding disorders in Pregnancy, April 2017

2. The Diagnosis and Management of Von Willebrand Disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology: BJH Guideline, 2014,**167**, 453-465

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