

Management dei disordini emorragici congeniti in gravidanza

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Obstetric Hemorrhage and Maternal Deaths

- Abruptio placenta – 19 percent
- Uterine rupture – 16 percent
- Uterine atony – 15 percent
- Coagulation disorder – 14 percent
- Placenta previa – 7 percent
- Placenta accreta – 6 percent
- Retained placenta – 4 percent

Chichaki, et al, 1999

Postpartum Hemorrhage

Etiology is linked to **Risk Factors**

Bleeding from Placental Implantation Site

- **Hypotonic myometrium—uterine atony**
- **Some general anesthetics**
- **Poorly perfused myometrium**
- **Over distended uterus**
- **Prolonged labor**
- **Very rapid labor**
- **Oxytocin-induced or augmented labor**
- **High parity**
- **Uterine atony in previous pregnancy**
- **Chorioamnionitis**
- **Retained placental tissue**
- **Avulsed cotyledon, succenturiate lobe**
- **Abnormally adherent—accreta, increta, percreta**

Postpartum Hemorrhage

Etiology is linked to **Risk Factors**

Trauma to the Genital Tract

- **Large episiotomy, including extensions**
- **Lacerations of perineum, vagina or cervix**
- **Ruptured uterus**

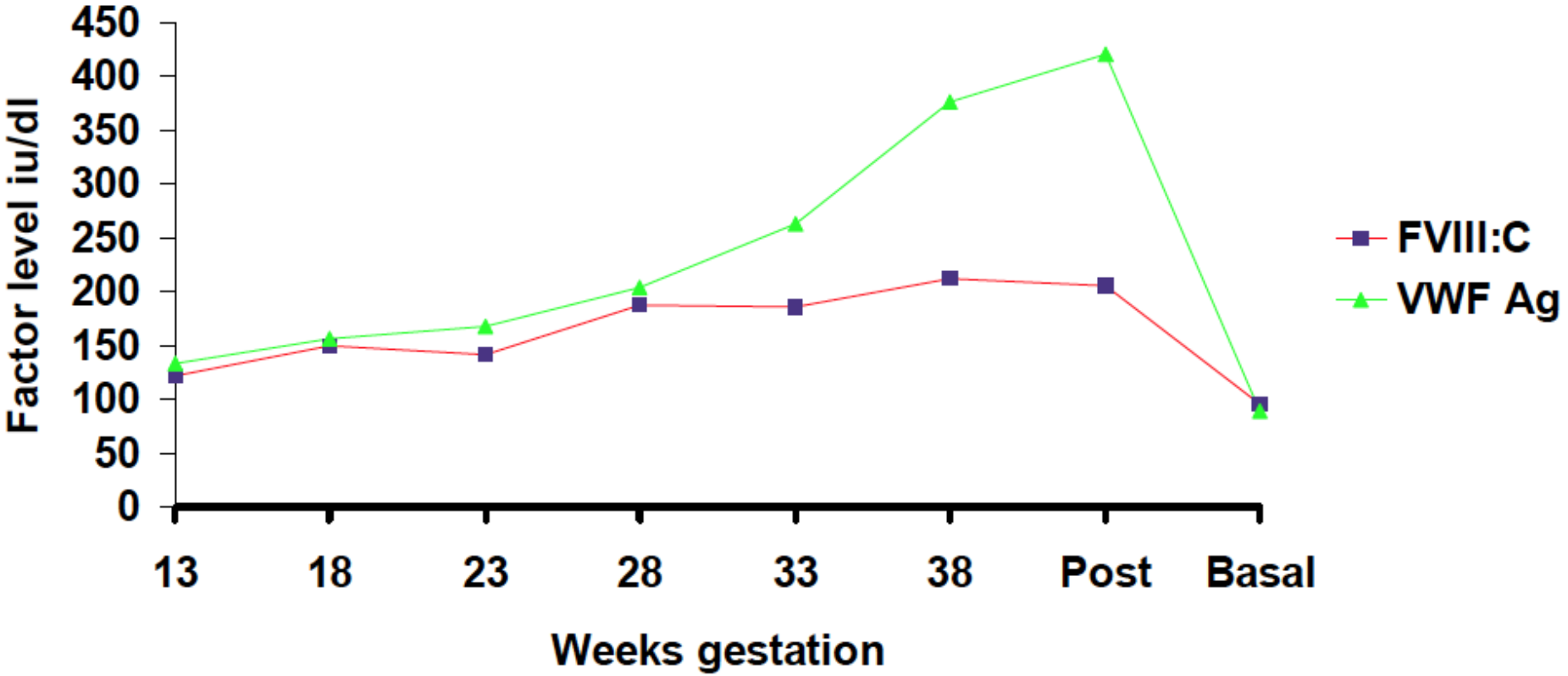
Coagulation Defects **Intensify all of the above**

Table 2
Haemostatic changes during normal pregnancy.

Clotting factors	Changes
Fibrinogen	Increase
FVII	Increase
FVIII	Increase
FX	Increase
FXII	Increase
VWF	Increase
FII	No significant change
FV	No significant change
FIX	No significant change
FXI	Inconsistent
FXIII	Decrease

F, factor; VWF, von Willebrand factor.

VWF and FVIII during pregnancy



Causes of Maternal Deaths due to Hemorrhage

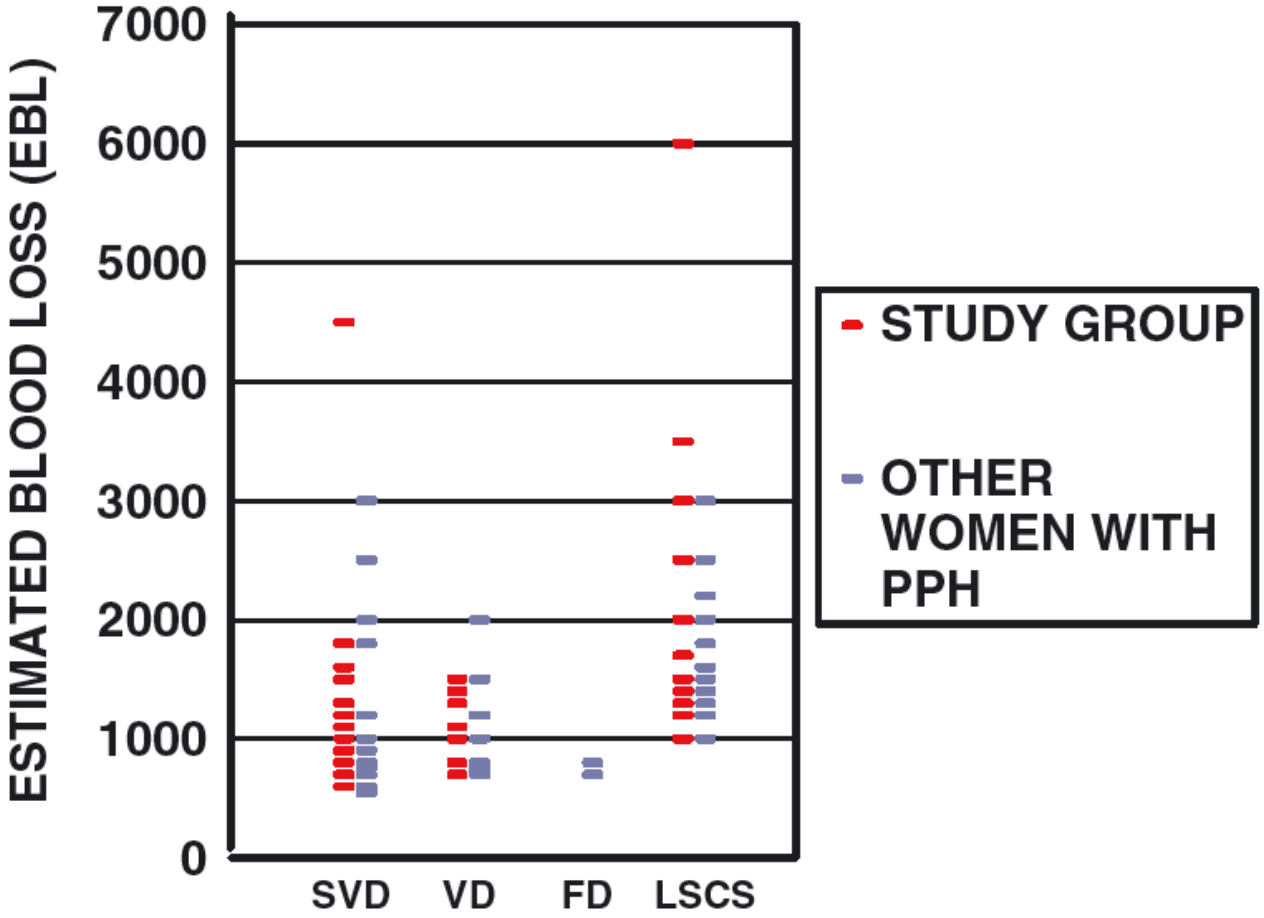
- Inadequate resources and personnel – for example, home delivery attempts.
- Failure to prepare for obstetric hemorrhage – for example, no IV site started on admission.
- Delay in recognition of hemorrhage.
- Delay in treatment of hemorrhage.
- Treatment failures.

Risk factors for PPH

Table 1. SOGAP assessment of risk factors for postpartum haemorrhage.

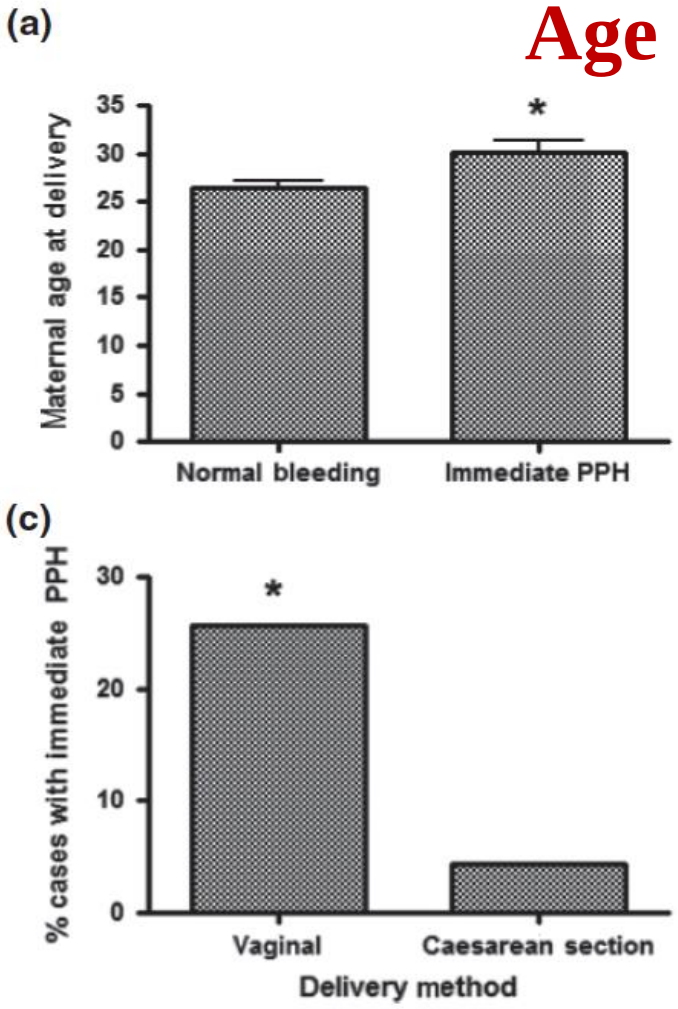
	Approximate OR for PPH
Placental abruption	13
Placenta praevia	12
Emergency caesarean	9
Elective caesarean	4
Retained placenta	5
Episiotomy	5
Multiple pregnancy	5
Pre-eclampsia	4
Multiparity	3
Previous PPH	3
Operative vaginal delivery	2
Prolonged labour (>12 h)	2
Big baby (>4 kg)	2
Obese	2
Pyrexia in labour	2

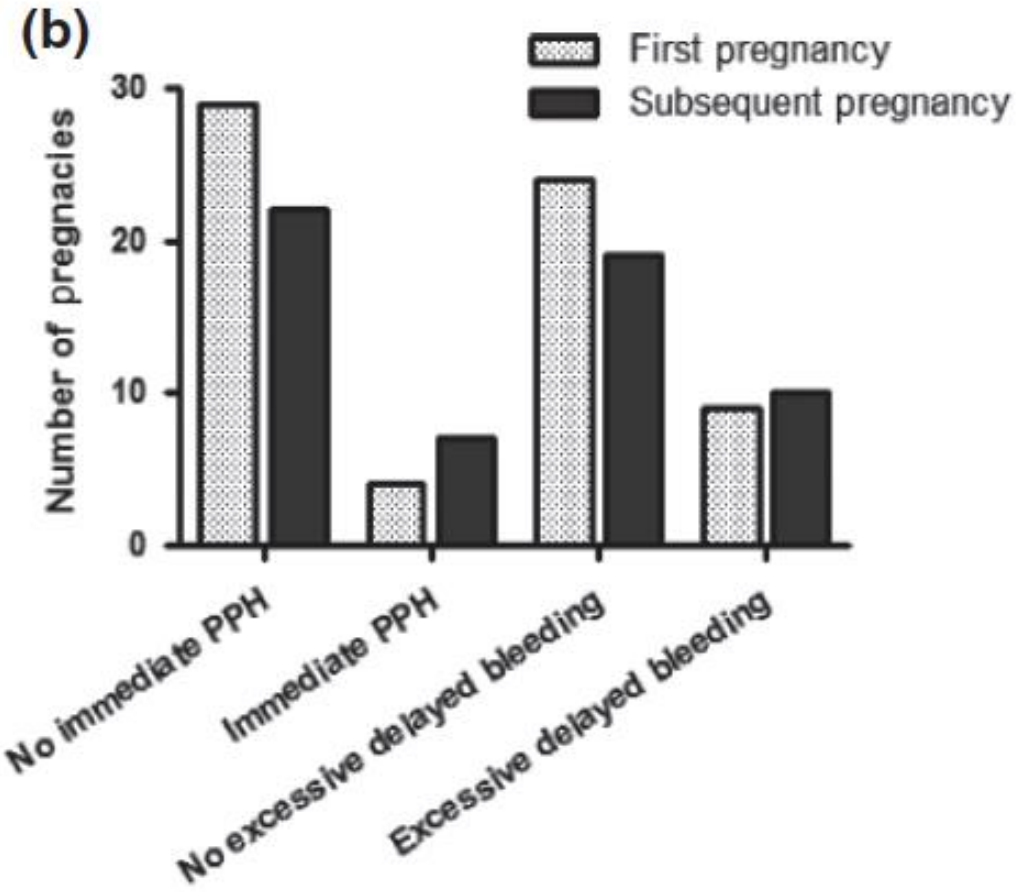
CHEE Y. L. et al, Haemophilia 2012



KADIR RA et al. Haemophilia 2007

Age as risk factor for PPH





HAWKE L et al, Haemophilia 2016

Women with VWD were more likely to experience:

- **antepartum bleeding** **OR 10.2**
- **postpartum bleeding** **OR 1.5**
- **risk of requiring a transfusion** **OR 5.0**

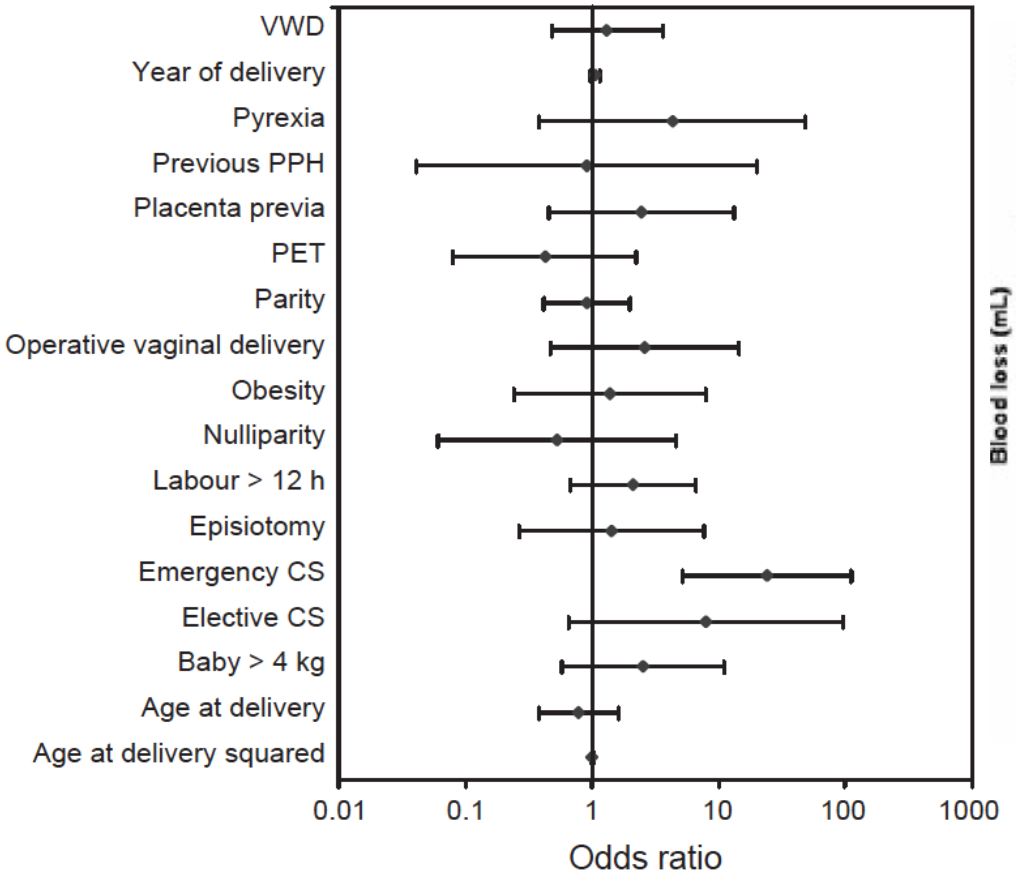
James AH, Jamison G. J Thromb Haemost 2007

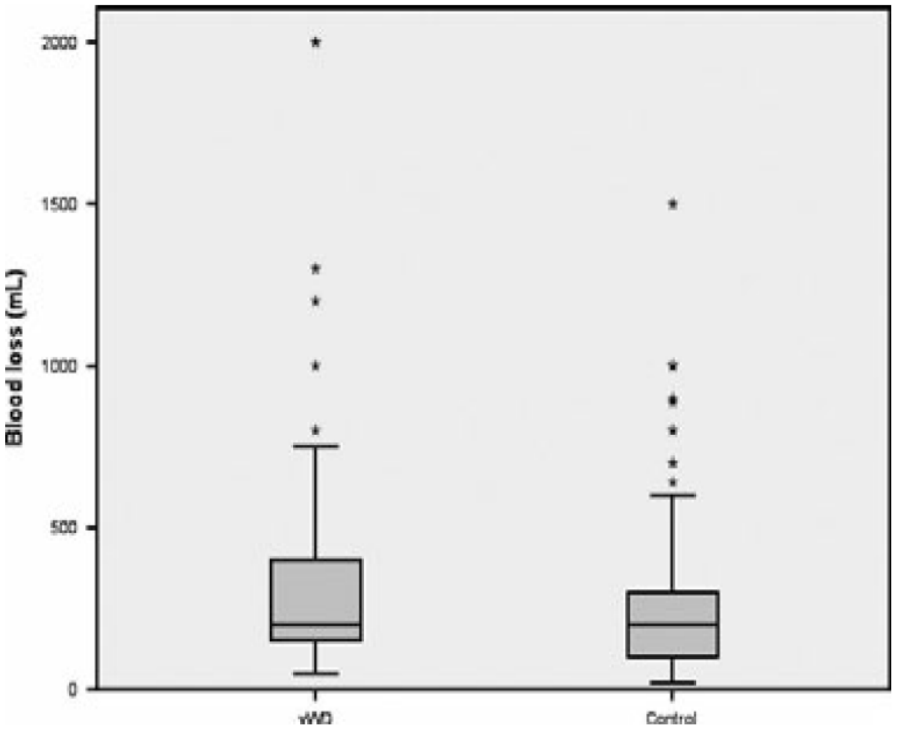
Women with VWD were more likely to experience:

- **Primary postpartum hemorrhage** **18-22%**
- **Secondary postpartum hemorrhage** **20-28%**

Hanna W, et al. Blood 1981
Kadir RA et al. BJOG 1998

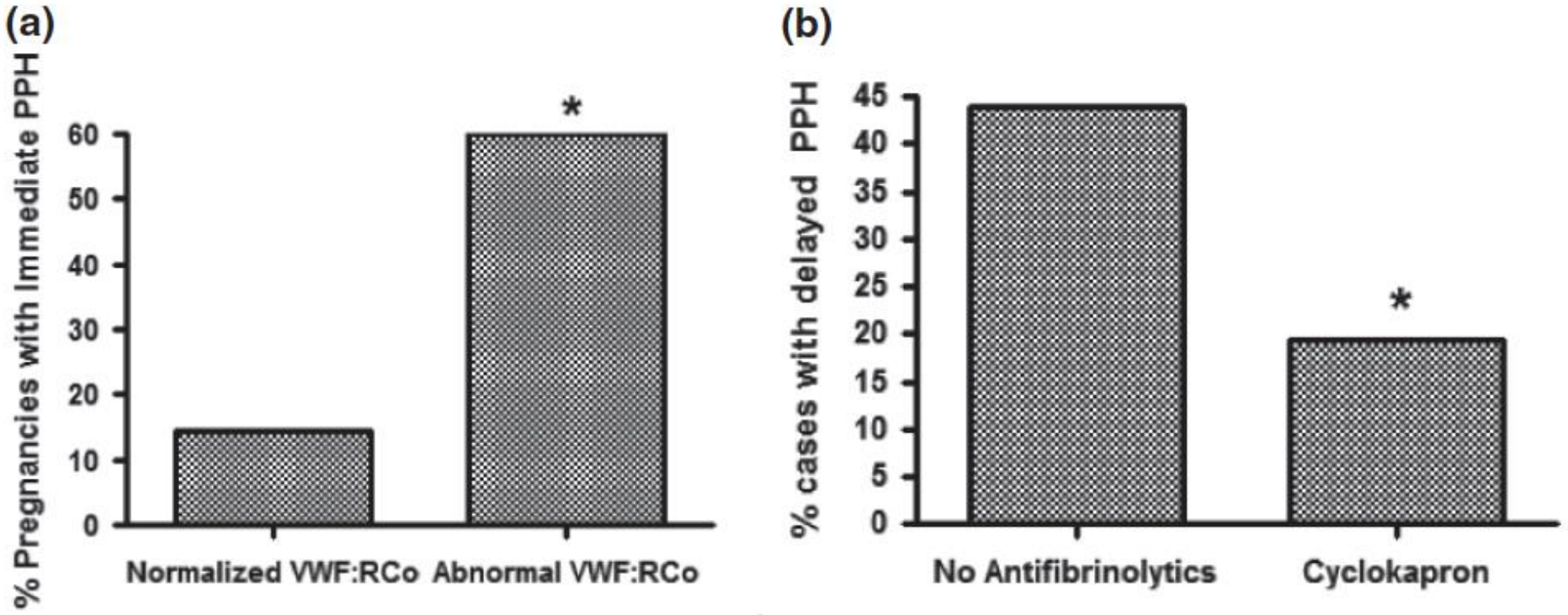
VWD in itself may not be a significant risk factor for PPH





CHEE Y. L. et al, Haemophilia 2012

Therapy for von Willebrand disease



HAWKE L et al, Haemophilia 2016

Therapy for von Willebrand disease

- DDAVP First line for Type I
- Many women with Type I improve their FVII and vWD levels to normal without needing DDAVP
- Give 30 min pre-procedure, lasts 8-10 hrs, tachyphylaxis with repeated doses
- Goal to maintain vWF:Ag and RiCoF > 50 IU/L
- Plasma derived vWF concentrate
    - Repeat doses at 8-12 hours
    - All types, Follow vWF:RCo levels
- Cryoprecipitate
    - All types, but last line

DDAVP - Desmopressina

Benché l'effetto ossitocico di Desmopressina sia trascurabile, si consiglia di non somministrare il farmaco in gravidanza se non in caso di effettiva necessità e solo sotto diretto controllo medico.
I risultati delle analisi del latte di madri nutrici trattate con una dose elevata di Desmopressina (300 µg per via endonasale) indicano che le quantità di Desmopressina che possono essere apportate al bambino col latte materno sono notevolmente inferiori a quelle necessarie a esercitare un effetto sulla diuresi e sull'emostasi.

Sebbene l'effetto ossitocico della desmopressina sia praticamente trascurabile, la somministrazione a donne gravide è bene sia riservata ai casi di effettiva necessità e comunque sotto diretto controllo medico.
Poiché non è noto se la desmopressina sia secreta con il latte umano è opportuno esercitare cautela nella terapia delle donne in allattamento.

DDAVP - Desmopressina

Studi di riproduzione nei ratti e nei conigli con dosi di oltre 100 volte superiori a quelle impiegate nell'uomo, non hanno evidenziato effetti dannosi della Desmopressina sul feto.

Uno sperimentatore ha riportato 3 casi di malformazioni in bambini nati da madri affette da diabete insipido e trattate con Desmopressina per via endonasale durante la gravidanza.

Tuttavia molte altre pubblicazioni relative a oltre 120 casi indicano che donne trattate durante la gravidanza con Desmopressina, hanno dato alla luce bambini normali.

Inoltre **una revisione clinica relativa a una casistica molto numerosa ha permesso di identificare 29 bambini che sono stati esposti a Desmopressina per tutta la gravidanza, senza evidenziare un aumento della percentuale di malformazioni nei nati.**

Women carrying Hemophilia were more likely to experience:

- **Primary postpartum hemorrhage** **22% (vs. 5-8%)**
- **Secondary postpartum hemorrhage** **11% (vs. 0.8%)**

El Refaey H & Rodeck C. Br Med Bull 2003;
Hoveyda F & MacKenzie IZ. BJOG 2001;
Kadir RA et al. BJOG 1997; Mauser Bunschoten EP, et al. Thromb Haemost 1988

Mode of delivery

The risk of ICH in relation to labour and delivery in neonates affected has been estimated to be 3.5–4%.

The optimal mode of delivery for male fetuses at risk is controversial

Vaginal delivery

Higher risk for:

- **ICH**

Cesarean Section

Higher risk for:

- **bleeding risks in the carrier mother**
- **complications in future pregnancies**

Women with FXI deficiency:

- Bleeding tendency is **variable, inconsistent and poorly correlated to factor levels** or the genotype.
- FXI 15 to 70 IU/dL **and no bleeding history** despite haemostatic challenge: vaginal delivery can be managed expectantly with treatment on standby in women.
- FXI 15 to 70 IU/dL **and a significant bleeding history** or no previous haemostatic challenge: tranexamic acid can be used to provide peripartum cover starting at the onset of labour.
- Replacement therapy may be required for caesarean section.
- FXI <10–20 IU/dL: replacement therapy with FXI concentrate is recommended for all modes of delivery.

Bolton-Maggs PH, et al. Haemophilia 2004.
Bolton-Maggs PH, et al. Thromb Haemost 1995.
Bolton-Maggs PH, et al. Lancet 1994. Ragni MV, et al. Blood 1985.

Table 1
Rarer factor deficiencies and their implications.[50]

Deficiency	Pregnancy complications	Treatment products	Pregnancy management	Anaesthetic implications
FI	Recurrent miscarriage APH, PPH, Thrombosis	FI conc.; Avoid cryoprecipitate, if possible; Fibrin glue, TXA	AF: FI conc prophylaxis DF: Avoid procedures in nn. Observe unless bleeding; Thromboprophylaxis if history thrombosis	AF: Possibly NA after FI conc & levels $>1\ g\ dL^{-1}$ DF: NA contraindicated; FI conc. only if bleeding for CD
FII	PPH	3 or 4 factor PCC; FFP	Reasonable to increase FII level to $>25\ IU\ dL^{-1}$	No reports in pregnancy
FV	Bleeding[51]	FFP	Reasonable to give FFP to raise level $>15\ IU\ dL^{-1}$	GA used for C/D in one case. NA probably CI
FVII	No reports of complications with full-term pregnancies. Haemorrhage with miscarriage	rVIIa; PTCC; FFP; Fibrin glue; TXA	1 case of continuous infusion of rFVIIa for elective CD[55]	rFVIIA allowed epidural in severe cases[55]
FX	Bleeding during pregnancy, preterm delivery	TXA; Fibrin glue; FFP; PCC; plasma exchange in one case[57]	FX increases in pregnancy Adverse pregnancy outcome may benefit with replacement – risk thrombosis	NA probably OK if FX levels $>20\ IU\ dL^{-1}$
FXI	PPH	FFP; FXI conc.; rFVIIa; TXA; Fibrin glue	VD: FXI level 15–70 $IU\ dL^{-1}$ + no bleeding history – watch & wait If same level + bleeding history – TXA × 3 days Severe FXI deficiency – FXI conc CD: as for VD	Reports of NA following FXI conc & normal levels[58]
FXIII	Miscarriage, PPH	FXIII conc; FFP; Cryoprecipitate	FXIII conc monthly infusions from diagnosis of pregnancy	NA CI

APH = antepartum haemorrhage; PPH = postpartum haemorrhage; TXA = tranexamic acid; AF = afibrinogenaemia; DF = dysfibrinogenaemia; conc = concentrate; NA = neuraxial anaesthesia; CI = contraindicated; CD = caesarean delivery; PCC = prothrombin complex concentrate; FFP = fresh frozen plasma; GA = general anaesthesia; VD = vaginal delivery

Before getting pregnant, carriers need clear and accurate information about:

- the chance of transmitting hemophilia to the child**.** Carriers of hemophilia have a 50 per cent chance of passing the disorder on to their children;
- the consequences, to both a female and a male child, of inheriting hemophilia;
- how hemophilia is treated, what care is available at a local level, and at what cost;
- **how pregnancy, labour, and delivery should be managed to reduce risks to both mother and child;**
- the options available for conception and prenatal diagnosis.

LABOUR AND DELIVERY: CONSIDERATIONS FOR MOTHER

- Clotting factor levels should be measured in the last trimester of pregnancy.
- If factor levels are low, treatment may be given during labour to reduce the risk of excessive bleeding during and after childbirth.
- Clotting factor levels may also determine whether a woman can receive local anesthesia (an epidural).

POSTPARTUM CARE: CONSIDERATIONS FOR MOTHER

- After delivery, a carrier's circulating clotting factor goes back down to her pre-pregnancy level and the chance of bleeding is at its highest.
- Carriers are at risk of PPH for up to six weeks after childbirth and should be advised to see their doctor immediately if bleeding is excessive during this period.
- Treatment may be recommended as a preventative measure, especially in carriers with low clotting factor levels.

Therapy for hereditary bleeding disorders

Table 4
Therapeutic options for women with inherited bleeding disorders in pregnancy.

Bleeding disorder	Preferred therapeutic option	Other options
VWF	Desmopressin or VWF-containing concentrates	Platelet (type 2B) rFVIII or FVIII concentrate (type 2N)
Carriers of haemophilia A	Desmopressin or rFVIII	FVIII concentrate
Carriers of haemophilia B	rFIX	FIX concentrate
Fibrinogen abnormalities	Fibrinogen concentrate	SD plasma
Prothrombin(II) deficiency	PCC	SD plasma
FV deficiency	SD plasma	SD plasma
FV and FVIII deficiency	SD plasma rVIII	FVIII concentrate
FVII deficiency	rVIIa	FVII concentrate
FX deficiency	PCC	SD plasma
FXI deficiency	FXI concentrates or Tranexamic acid	SD plasma rVIIa
FXIII deficiency	FXIII concentrates	SD plasma
VKCFD	Vitamin K	SD plasma PCC

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

Pregnancy is not the best time to start discussions and testing!!!