Approccio terapeutico al paziente con malattia di Von Willebrand

Eugenia Biguzzi, MD

Centro Emofilia e Trombosi A. Bianchi Bonomi

Milano

VWD

- VWD 1: quantitative deficiency, normal multimers
  - 1C (Vicenza, increased clearance, presence of ULM)
- VWD 2: qualitative deficiency
  - 2A: loss of HMWM
  - 2B: increased affinity for gp1b, loss of HMWM
  - 2M: normal HMWM
  - 2N: reduced binding to FVIII
- VWD 3: severe quantitative deficiency, loss of HMWM

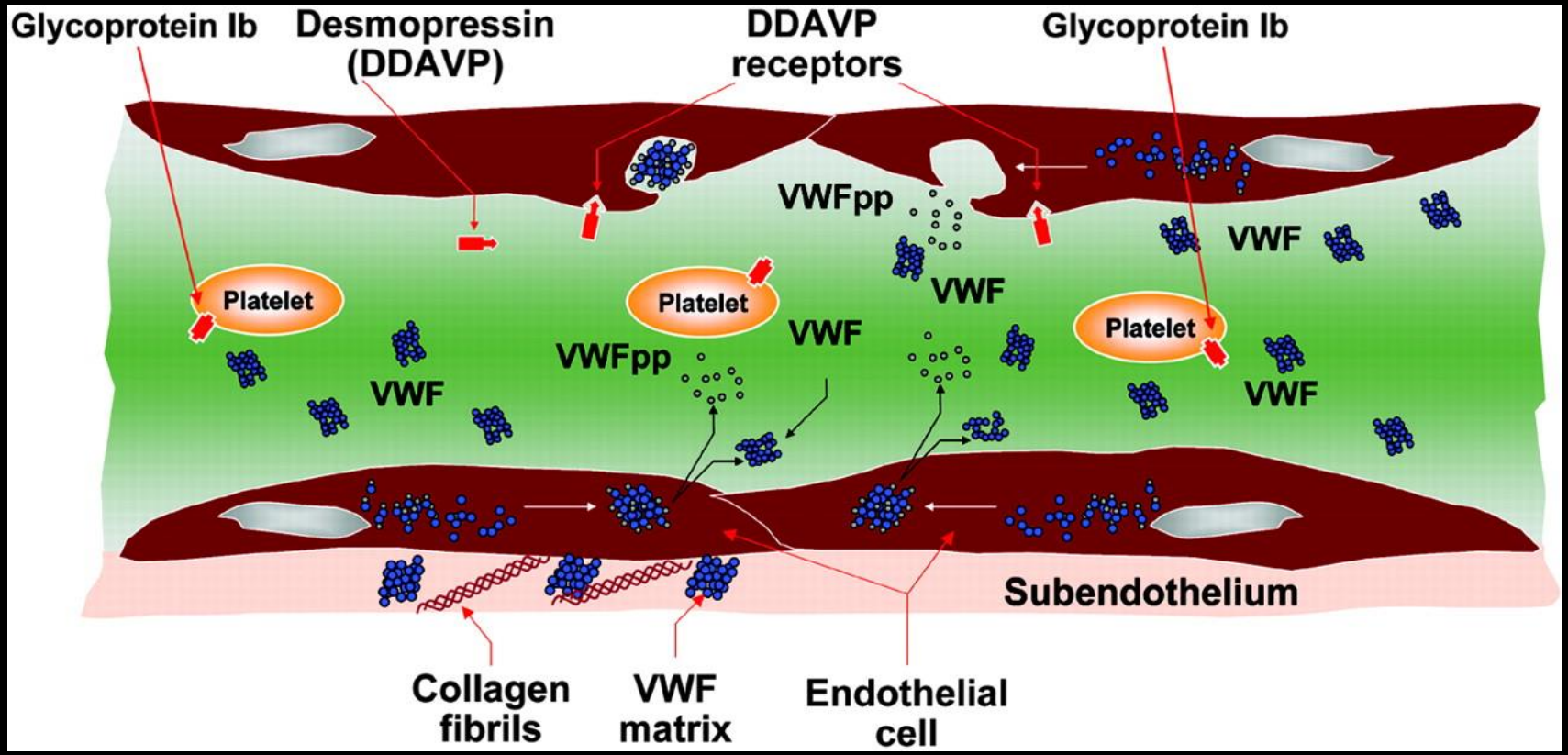
VWD: therapy

- Correction of VWF levels
  - DDAVP
  - concentrates
- Adjunctive therapy
  - Tranexamic acid
- Women issues
  - Menorrhagia
  - Pregnancy

DDAVP, desmopressin
(1-desamino-8-D-arginin vasopressin)

- Synthetic derivative of the human antidiuretic hormone vasopressin
- It raises FVIII and VWF plasma levels (2-3 folds, secretion from Weibel-Palade bodies of the endothelial cells)

DDAVP, desmopressin
(1-desamino-8-D-arginin vasopressin)



Federici Blood 2006;108:3229-3230

DDAVP, desmopressin
(1-desamino-8-D-arginin vasopressin)

- Test to evaluate response: evaluate FVIII and VWF after 1 hour and 4 hours
- Dose: 0.3microg/kg (intravenous or subcutaneous), generally every 24 hours;
- Capped dose 15 or 20microg for patients >50kg *(Siew et al 2014)*
- Commercial preparations: Emosint 4microg, Emosint 20microg, Minirin 4microg
- Immediate side effects: flushing, headache, hypotension/hypertension
- Side effects after repeated doses: hyponatremia and seizures, tachyphylaxis

type of VWD

- VWD 1: quantitative deficiency, normal multimers
  - 1C Vicenza, increased clearance, presence of ULM)
- VWD 2: qualitative deficiency
  - 2A: loss of HMWM
  - 2B: increased affinity for gp1b, loss of HMWM
  - 2M: normal HMWM
  - 2N: reduced binding to FVIII
- VWD 3: severe quantitative deficiency, loss of HMWM

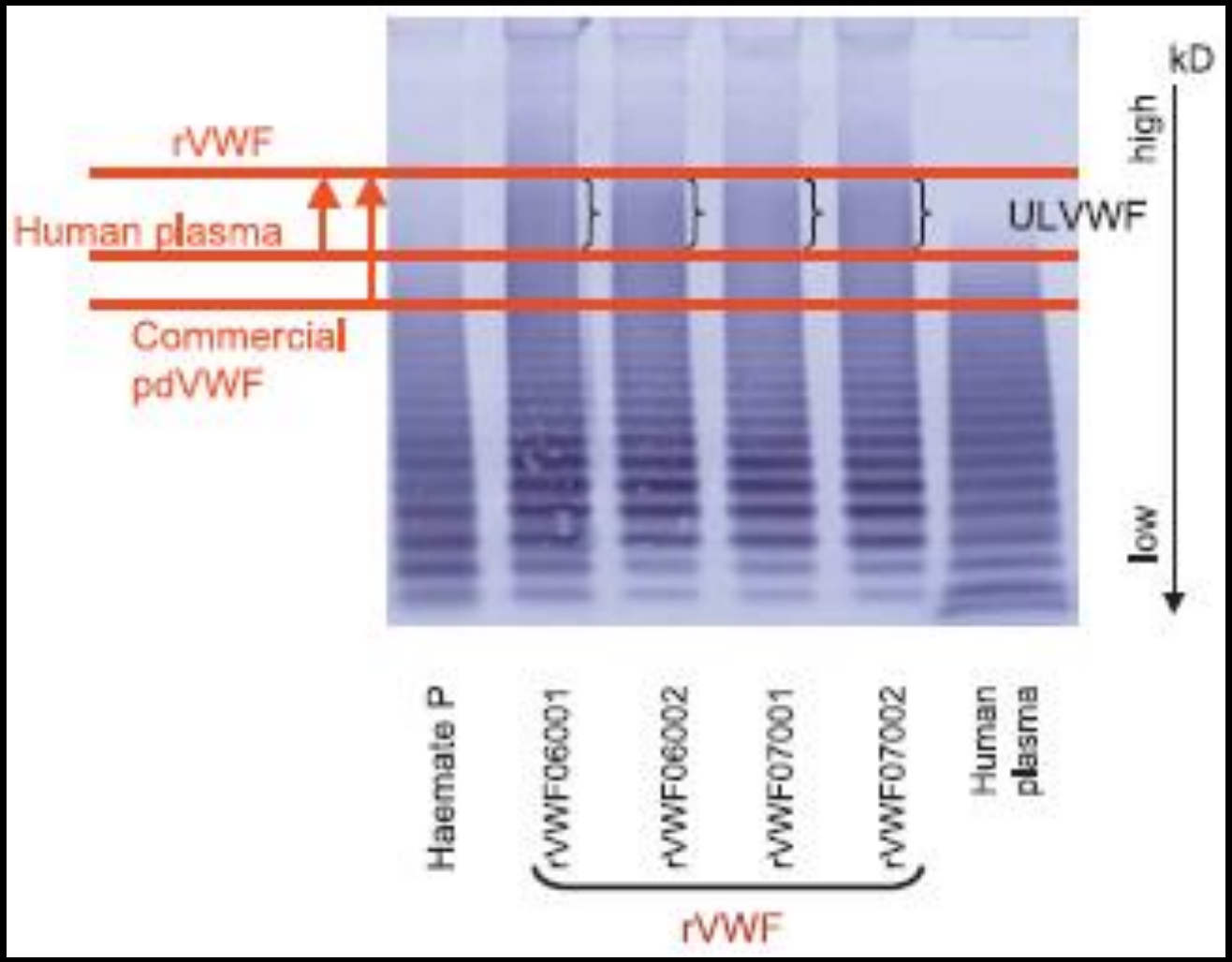
DDAVP response

- usually good
  - very good response that is lost after 2 hours, limited use
  - 2A: poor response
  - 2B: controindicated
  - 2M: variable response
  - 2N: good response but short, limited use
- not indicated

FVIII/VWF concentrates

Product	Purification	Viral inactivation	VWF:RCo /FVIII
Haemate-P, CSL	Multiple precicipation	Pasteurization (60°C, 10h)	1.04
Fanhdi/Alpha nate, Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72h)	2.45
Wilate, Octapharma	Ion exchange + affinity	S/D + dry heat (100°C, 2h)	1.0
Wilfactin, LFB	Ion exchange + affinity	S/D, 35nm filtration + dry heat (100°C, 2h)	≈50
rVWF, Baxter	rVW coespressed with rFVIII in CHO cells; rVWF +rfurin to remove propeptide; purification		Only VWF

FVIII/VWF concentrates:multimers prophile



Bleeding events and VWF levels

Clinical situation	**Target trough level of VWF**	**Desmopressin responsive:** DDAVP 0.3mcg/kg every 12-24h until bleeding stops	**Desmopressin unresponsive:** 30-50U/kg FVIII/VWF concentrate immediately, then every 24h until bleeding stops	Tranexamic acid: 15-25mg/kg every 8-12 hourr
Clinically relevant non-major bleeding	>30	X	X	X
Major (life-threatening) bleeding	>50		X	X
Tooth extraction	>50	Single dose	Single dose	X
Minor surgery	>30	X	X	X
Major surgery	>50		X	X

Prophylaxis: from hemophilia A to VWD

- It is logical to translate the success of prophylaxis obtained in hemophilia A to severe VWD: prophylaxis could be implemented early in life in a home setting, and prevention of bleeding and its consequences could be possible
- Nevertheless, the documented experience with long-term prophylaxis in VWD is limited

PRO.WILL: preliminary data

(Federici, Haemophilia 2007)

11 PATIENTS

type 3 (n=5; 4 pts for joints bleeding, 1 for GI bleeding)

type 2A (n=4, GI bleeding)

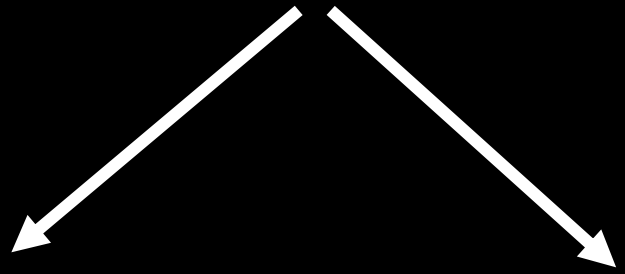
type 2M (n=1, GI bleeding)

type 1 (n=1, GI bleeding)

prophylaxis

3-15

months



8 PATIENTS

complete bleeding prevention

3 PATIENTS

reduced hospitalization

Von Willebrand Disease Prophylaxis network (VWD PN): VWD International Prophylaxis Study (VIP)

(Abshire et al, update Haemophilia 2013)

61 patients enrolled

analysis: 59 patients (10 countries, from 2008 to 2011)

Retrospective design

Median age 22.4ys (2.3-77.2)

type 3 (n=34) ; type 2 (n=20) ; type 1 (n=5); 2 excluded

→ Median time on prophylaxis

2.2 ys

32 PATIENTS

bleeding episodes/year prior to prophylaxis 12 (IQR 6-24)

bleeding episodes/year during prophylaxis 3.6 (IQR 0.96-9.4)

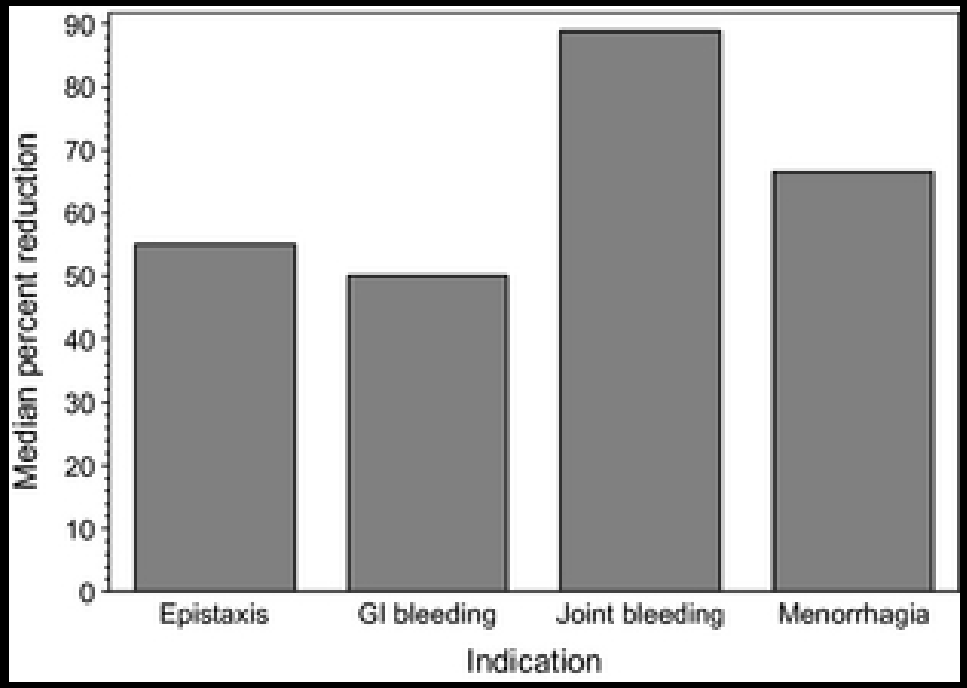
1 PATIENT

inhibitor development

(after 48 exposure days)

Von Willebrand Disease Prophylaxis network (VWD PN): VWD International Prophylaxis Study (VIP)

(Abshire et al, Haemophilia 2012)



Outcomes measured as percent reduction in bleeding within individuals during prophylaxis, according to primary indication for treatment.

Prohpylaxis escalation in severe VWD

(Abshire et al, JTH 2015)

13 patients enrolled

analysis: 11 patients (5 VWD3; 6 VWD2A)

prospective design, Median age 34.6ys (3.1-80.6); ABR 25.0 (IQR 12-51.2)

Time on prophylaxis: 1 year

ABR 4.0 (IQR 0-27.7)

TREATMENT LEVEL 1

(50U Rco/kg once/week)

4 epistaxis

(2 type 3, 2 type 2A)

TREATMENT LEVEL 2

(50U Rco/kg twice/week)

1 epistaxis, 1 GI, 1 joint

(1 type 2A , 2 type 3)

TREATMENT LEVEL 3

(50U Rco/kg 3/week)

1 epistaxis, 1 GI, 1 joint

(1 type 3, 2 type 2A)

+ 1 patient (type 2A): 50U/kg every other day

Prophylaxis in VWD: open questions

- Indications to begin (VWF & FVIII:C levels or bleeding severity?)
- When to begin (young age for type 3 with joints bleeds or frequent mucosal bleeding? older age for type 2 with frequent mucosal bleeds? fertile age for type 3 or type 2 women looking for pregnancy?)
- What frequency, what dosage, what concentrate (minimal VWF:Rco and FVIII:C before the next infusion? minimal VWF:Rco and FVIII:C levels between the infusions to avoid imprecision due to very low levels of VWF:Ricof?)
- When to stop (puberty for males with type 3? switching to oral oestrogens for young females at puberty?)
- Role of VWF/FVIII concentrates in GI bleeds (prevention of bleeding by manteining higher levels of VWF and FVIII:C? prevention of GI artero-venous malformations?)
- Inhibitor development (mutations predisposing to inhibitor development? Relation with factor dosage?); thrombotic complications

Severe VWD and menorrhagia

Severe = unresponsive to DDAVP (type 3, type 2, type 1)

Response to oral contraceptive treatment for menorrhagia	Type 3 n=23	Type 2 n=9	Type 1 n=12	TOTAL n=44
Treated	13	6	11	30
Good response N°	10	4	8	22
No response N°	0	1	2	3
Not reported N°	3	1	1	5

Foster on behalf of ISTH-SSC. Thromb Haemost, 1995

Menorrhagia and quality of life

	VWD	Other bleeding disorders	VWD
N°	**259 females** **type 2/3: 37 (14%)**	**59 females**	**97 males** **type 2/3: 37 (31%)**
Health related quality of life * **Mean (SD)**	**0.70 (0.27) §**	**0.78 (0.22)**	**0.77 (0.25)**

Women VWD Menarche - 45ys	Menorrhagia	No Menorrhagia
N°	**84**	**104**
Health related quality of life * **Mean (SD)**	**0.64 (0.28) §**	**0.82 (0.20)**

***** dead=0, perfect health=1; § significantly different $p<0.05$

Rae *et al*. Haemophilia, 2013

VWD and menorrhagia

- 423 women VWD ≥16ys
  - ✓ 64% type 1, 32% type 2, 4% type 3

- Menorrhagia: 81%
  - ✓ ≥ 2 symptoms: subjective excessive blood loss/ blood clots / iron therapy or blood transfusion / heavy menstrual flow that interferes with daily life / periods longer than 7 days

- Gynecologist consultation: 85%

- Some treatment for menorrhagia: 99% (68% hormonal therapy)

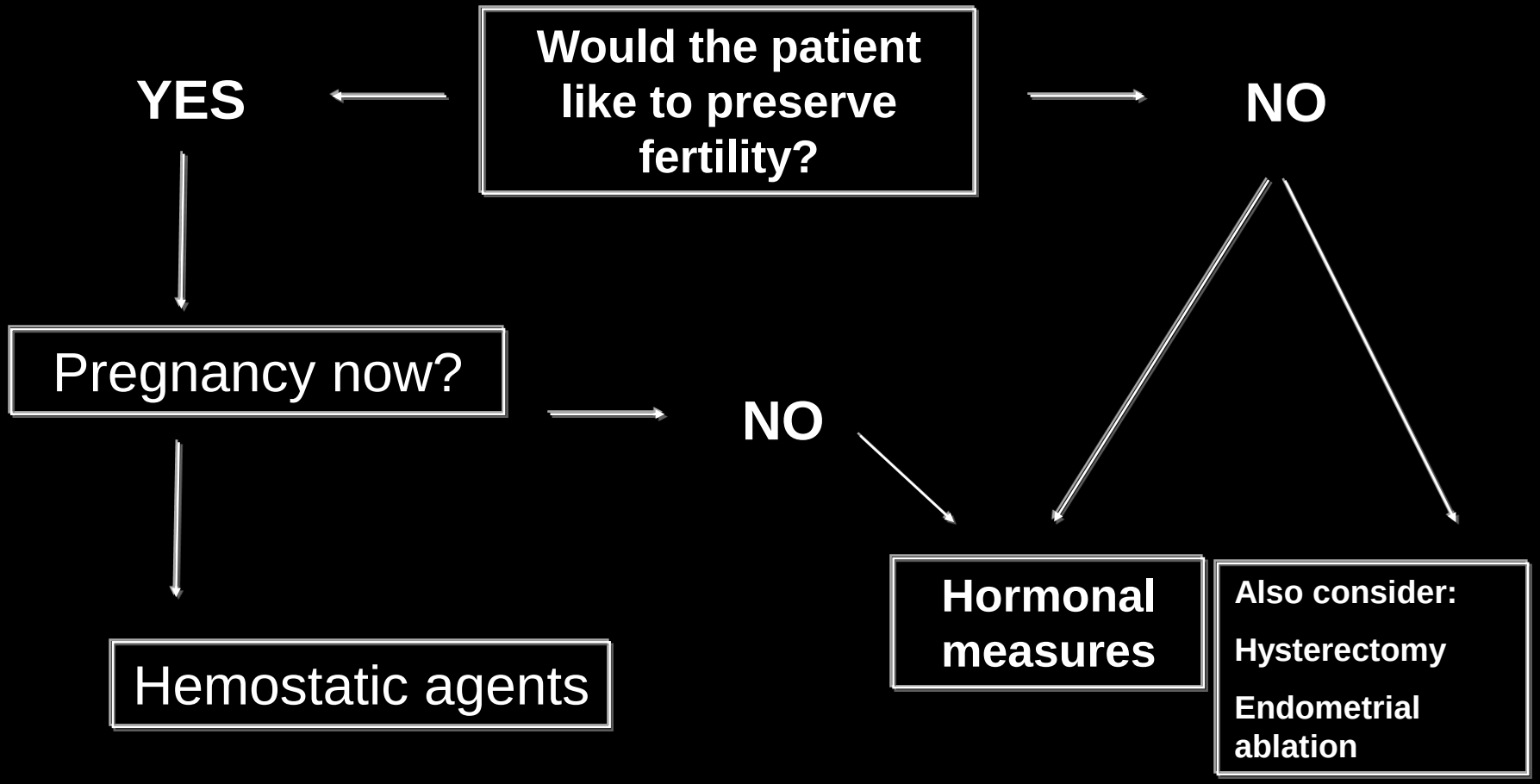
- Hysterectomy 20%

De Wee. Thromb Haemost, 2011

Women issues

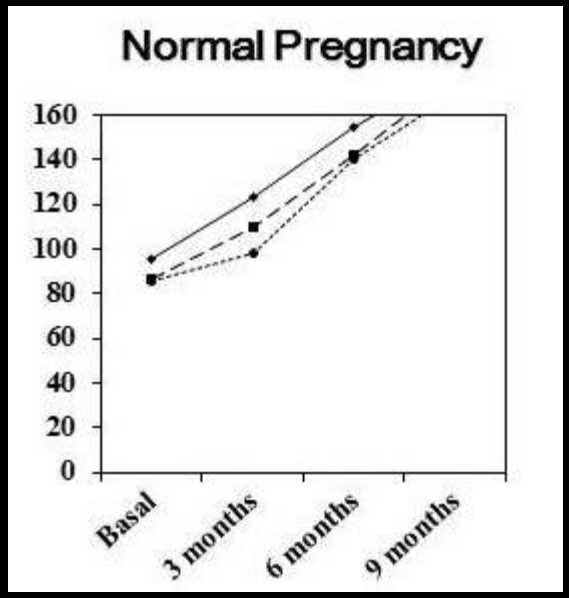
- Menorrhagia
  - Combined oral contraceptives
  - Levonorgestrel-releasing intrauterine device (Mirena) (Chi et al, 2011)
  - Prophylaxis with FVIII/VWF concentrate
  - Tranexamic acid
  - Endometrial ablation and histerectomy

VWD and menorrhagia: consensus on management



James *et al*. Am J Obstet Gynecol, 2009

VWF and normal pregnancy



♦ FVIII:C ; ■ VWF:Ag ; ●VWF:RCo (IU/dL)

Castaman. Mediterr J Hematol Infect Dis, 2013

Severe VWD and pregnancy

Severe = unresponsive to DDAVP (type 3, type 2, type 1)

	Type 3	Type 2	Type 1	TOTAL
N° women with pregnancy	11	7	13	31
N° pregnancies	15	13	41	69
Miscarriage	1	2	12	15
N° patients with miscarriage	1	2	5	8
Therapy* used at delivery	13/14	7/10	5/31	
Bleeding	3 (treated) +1 (not treated)	2 (treated)	10 (not treated)	

*Therapy: FFP, cryoprecipitate or FVIII concentrate

Foster on behalf of VWF-SSC, Thromb Haemost 1995

Natural course of post-partum hemorrhage in VWD

Enrollment and bleeding score before diagnosis of VWD

(clear autosomal dominant type 1VWD, confirmed in at least one family member)

POST-PARTUM BLEEDING SCORE				
	0 **no or trivial**	**1** **present requiring medical attention iron therapy**	**2** **dilatation suturing curettage blood transfusion**	**3** **hysterectomy**
Type 1 VWD **N=37**	**16 (43%)**	**9 (24%)**	**6 (16%)**	**6 (16%)**
Normal controls **N=105**	**102 (97%)**	**1 (1%)**	**2 (2%)**	**0**

Rodeghiero *et al*. J Thromb Haemost, 200

PPH risk in VWD

- Case-control study: 62 deliveries in 33 women with VWD (7 type 2, no type3), 124 controls (matched for age at delivery, parity and year of delivery); years: 1949-2005 (Aberdeen registry)
- PPH: blood loss ≥ 500ml
- The majority of patients did not receive DDAVP or factor replacement
- All VWD patients
  - ✓ PPH 19% VWD vs 12% controls
  - ✓crude OR for PPH: 1.62 (95% CI 0.75-3.49)
  - ✓adjusted* OR for PPH: 1.31 (95% CI 0.48-3.60)
- VWD patients (diagnosed before pregnancy, n=24)
  - PPH 29% VWD vs 12% controls
  - crude OR for PPH: 2.78 (95% CI 1.03-7.49)
  - adjusted OR for PPH: 3.41 (95% CI 1.07-10.9)

**adjusted for: placental abruption, placenta praevia, emergency cesarean, elective cesarean, retained placenta, episiotomy, multiple pregnancy, pre-eclampsia, multiparity, previous PPH, operative vaginal delivery, prolonged labour, big baby, obesity, pyrexia*

Chee *et al*. Haemophilia, 2012

PPH risk in VWD

- Pregnancy-related discharge codes years 2000-2003 (NIS: largest all-payer inpatient database)
- Aim of the study: to determine the incidence of bleeding events and other complications in women with VWD
- Deliveries = 16,824,897; deliveries & VWD = 4067
- OR for PPH → 1.5 (95% CI 1.1-2.0)
- OR for ante-partum bleeding → 10.2 (95% CI 7.1-14.6)
- OR for receiving a transfusion → 4.2 (95% CI 3.2-7.0)
- OR for perineal hematoma → 3.3 (95% CI 0.8-13.4)
- 5 deaths in VWD patients (123/100,000 vs 12.7/100,000)

James *et al*. J Thromb Haemost, 2007

VWD and pregnancy: a practical approach

- Diagnose VWD before pregnancy
- Test DDAVP before pregnancy
- Preconceptual counselling (VWD type 3)
- Discuss possible chorionic villus sampling/amniocentesis
- Evaluation of FVIII and VWF levels during pregnancy (week 28 and 34)
- Management plan for labour and delivery
- Cesarean section is not indicated because of VWD

- **Work in team (obstetrician, gynecologist, midwife, anesthetist)!**

Chorionic villus sampling/amniocentesis

- Case series: 32 women with low FVIII:C (years 1988-2002); 27 obligatory carriers of hemophilia with factor VIII deficiency + 5 type 1 VWD
- 20 chorionic villus sampling + 12 amniocentesis FVIII:C median value 18 U/dL; range, 10-35 U/dL
- Avoid excessive fluid intake and control body weight
- FVIII:C after DDAVP median 60 U/dL (range, 40-121 U/dL)
- No abnormal bleeding; side effects: mild facial flushing and headache

DDAVP can be used during the first and second trimester of pregnancy; it is safe during invasive procedures that increase per se the risk of miscarriage.

No clinical sign of water intoxication or body weight increase in these women, who were warned to restrict fluid intake.

Mannucci. Blood, 2005

Delivery guidelines (I)

• Monitor factor levels (VWF:Ag, VWF:RCo and FVIII:C) at the beginning of pregnancy, 28 and 34 weeks and prior to invasive procedures

• Prophylactic treatment should be given when FVIII:C or VWF:Rco levels are <50% to cover invasive procedures and delivery

• Desmopressin can be used in normal pregnancy. Close monitoring for water retention must accompany its use

• Women with type I VWD generally do not require prophylactic treatment for delivery. In type 2 VWD, treatment is required for operative delivery or if there is perineal trauma. Women with type 3 VWD require treatment for all types of delivery.

• Epidural anaesthesia can be offered for use in majority of women with type 1 VWD whose VWF:RCo is >50%. It should be carried out by an experienced anaesthetist. It is generally not recommended for use in type 2 or 3 VWD.

• Women with VWF:RCo <50% should receive prophylactic treatment at the onset of labour or prior to planned caesarean section.

Lee. JBH, 2006; Chi. BPRCOG, 2012

Delivery guidelines (II)

- Fetuses affected with bleeding disorders are at higher risk of cranial bleeding during labour and delivery: fetal scalp electrodes and fetal blood sampling should be avoided

- Vacuum extraction, mid-cavity or rotational forceps delivery and prolonged second labour, especially during the second stage, should be avoided

- Inherited bleeding disorder is not an indication for cesarean section, but early recourse to it should be considered to minimize the risk of neonatal bleeding complications

- Factor levels should be monitored postdelivery and prophylaxis given to maintain VWF:RCo and FVIII levels >50% for at least 3 days, or 5 days following caesarean section. Tranexamic acid or COC pill should be considered to control prolonged and/or intermittent secondary PPH

Lee, 2006; Chi, 2012

Peripartum use of DDAVP

- 31 pregnancies in 23 women (6 type 1, 6 type 1 Vicenza, 9 type 2A, 2 type 2N); 14 primiparous
- DDAVP test performed before pregnancy
- Basal levels: VWF:RCo <10% in 17/21 (type 2N excluded); FVIII:C <30% in 17/23
- 5 no anti-hemorrhagic prophylaxis → no bleeding
- 22 DDAVP (1-3 doses in the first 48 hours; 1 dose in 4; 2 doses in 13; 3 doses in 5 women with episiotomy)
- 4 FVIII concentrate (in one case because of bleeding albeit DDAVP):
  - ✓ 2 women with type 2A, VWF:RCo 3% (p. V1665E), delayed bleeding in one woman
  - ✓ 2 women with type 1 and VWF:RCo <5%: one woman first treated with DDAVP and then with concentrate (second delivery with DDAVP, no bleeding); one woman excessive bleeding (lochia), treated with tranexamic acid
- **No analgesia!**

Castaman *et al*. Haematologica, 2009