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# VON WILLEBRAND FACTOR IN PREGNANCY

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# Bleeding risk in women during "reproductive life"

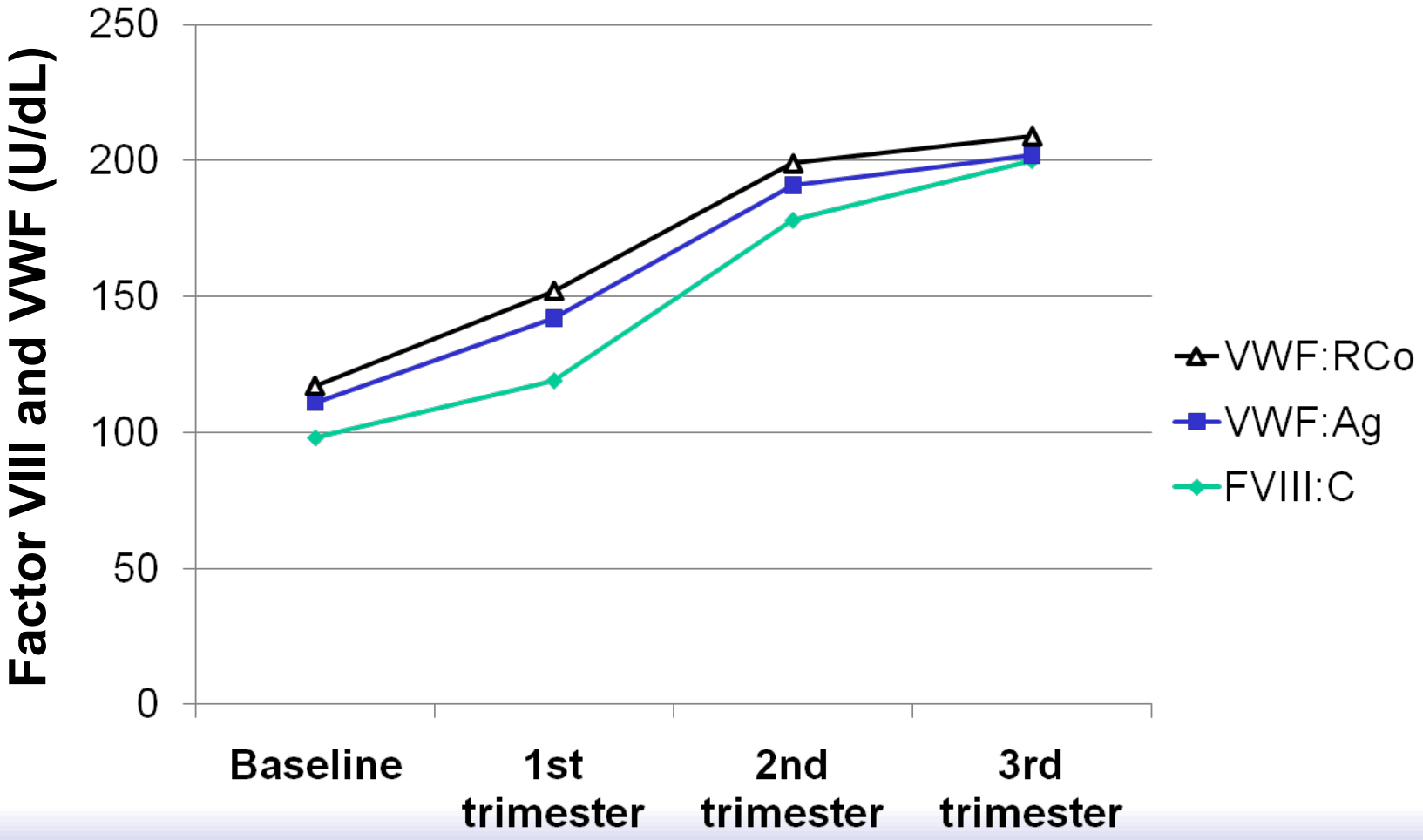
- Menstruation → Menorrhagia
- (Ovulation) → Hemoperitoneum
- Pregnancy → Miscarriage
  Retroplacental hematoma
  Vaginal bleeding
- Peri-partum → Delivery (PPH)
  Post-partum bleeding

# Changes of hemostasis in normal pregnancy

- Increased concentrations of fibrinogen, FVII, FVIII, FX and *VWF*
- FII, FV and FIX relatively unchanged
- Free PS reduced (increased levels of C4BP)
- Plasminogen activator inibitor type 1 increased

**Hypercoagulable state of pregnancy**

# FVIII/VWF changes in normal pregnancy



# Bleeding risk in VWD women during "reproductive life"

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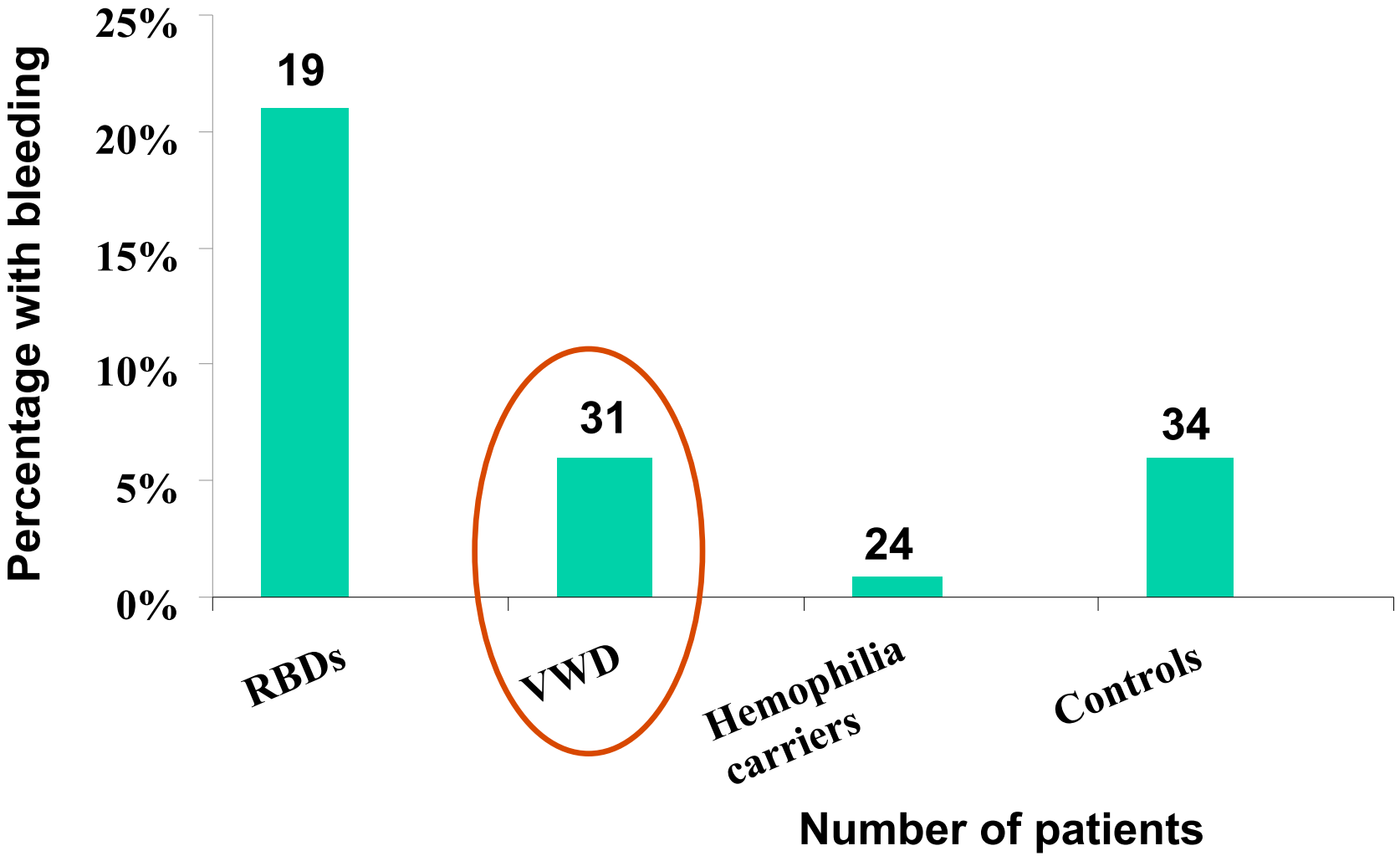
# Risk of miscarriage and bleeding during pregnancy in von Willebrand disease

- Case-control study: VWD 15 % vs 9 % controls (P = 0.05) (Kirtava 2003)
- Retrospective study in DDAVP-unresponsive VWD women 22 % (Foster 1995)
- Similar to normals in 182 Iranian women with type 3 VWD (Lak, 2000)
- Case-control study of 4,067 deliveries in women with VWD in USA (James, 2007), 10-fold higher risk of antepartum bleeding, but not:
  - placental abruption
  - preterm delivery
  - fetal growth restriction
  - stillbirth

# Bleeding during pregnancy in inherited coagulation disorders




Siboni 2009

# Bleeding risk in VWD women during "reproductive life"

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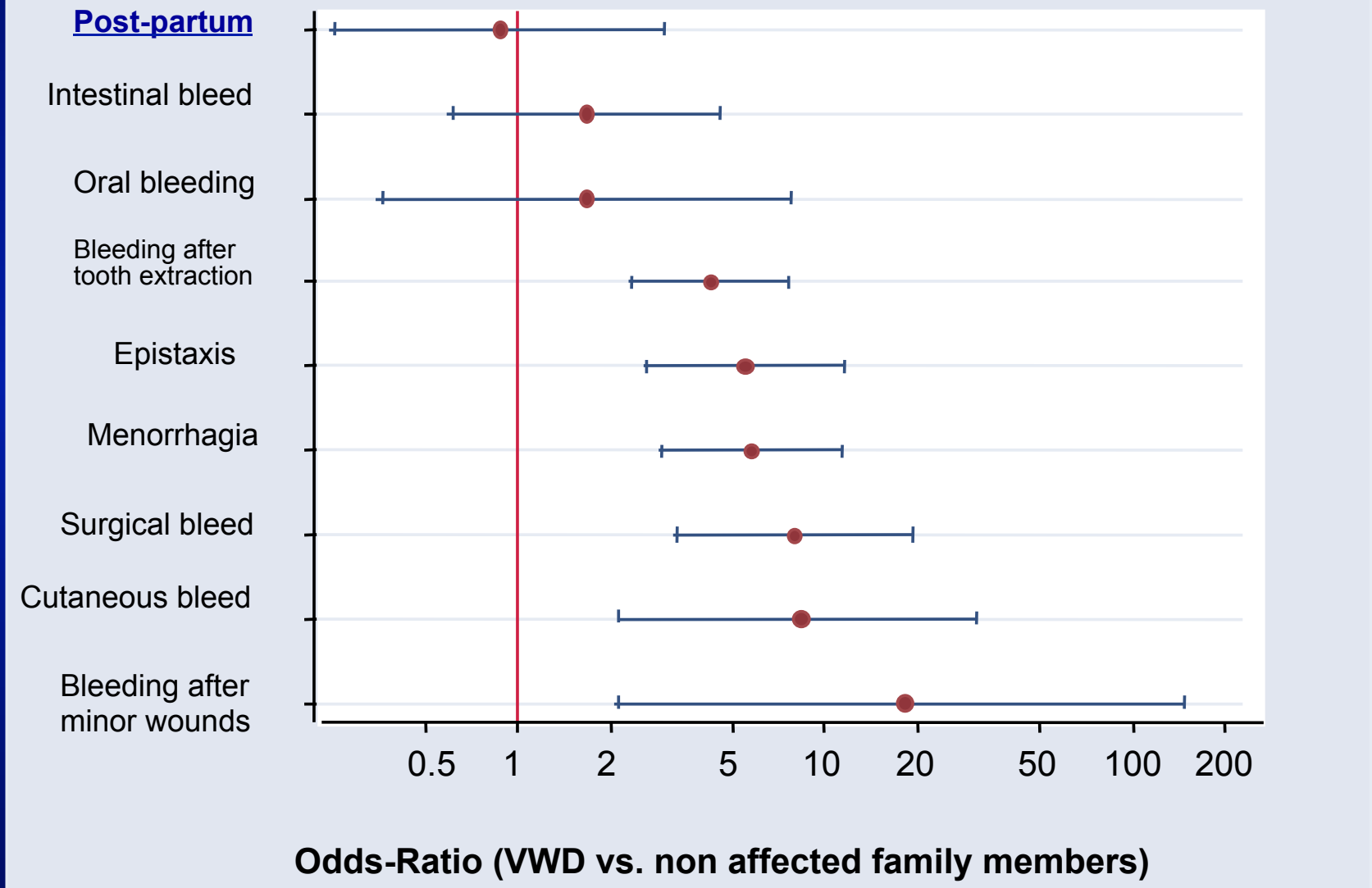
# Risk of bleeding at delivery in von Willebrand disease

- Case-control study type 1 VWD (Kouides 2000):
  - VWD 31 % vs 10 % controls
  - VWD 17 % vs 3 % controls received blood transfusion
- Case-control study (4,067 deliveries in VWD, James 2007):
  - OR 1.5 (95%CI 1.1 - 2) for bleeding
  - OR 4.7 (95%CI 3.2 – 7) being transfused
- Risk of perineal hematoma

# (MCMDM-1 VWD, JTH 2006)



# IMS-2005 (Diagnostic criteria for type 1 VWD)
# Symptom scores (I)
## (before diagnosis)

### Epistaxis
0 = no or trivial
1 = present
2 = packing/cauterization
3 = transfusion/replacement

### Cutaneous symptoms
0 = no or trivial
1 = petechiae/bruises
2 = hematomas
3 = medical consultation

### Minor wounds
0 = no or trivial
1 = present ( 1-5 episodes/year)
2 = medical attention
3 = surgical / blood transfusion

### Oral cavity bleeding
0 = no or trivial
1 = present
2 = medical attention
3 = surgical / blood transfusion

### Gastrointestinal bleeding
0 = no or trivial
1 = present
2 = medical attention
3 = surgical / blood transfusion

### Post-partum hemorrhage
0 = no or trivial
1 = present, medical attention, iron therapy
2 = blood transfusion, dilatation, curettage, suturing
3 = hysterectomy

# Post-partum bleeding in type 1 VWD (IMS, JTH 2005)

(*Before Diagnosis*)

| | Post-partum Bleeding Score* | | | |
|---|---|---|---|---|
| | 0<br>no or trivial | 1<br>Present, medical attention, iron therapy | 2<br>Blood transfusion, dilatation, curettage, suturing | 3<br>Hysterectomy |
| Type 1 VWD (n= 37) | 16<br>(43.2 %) | 9<br>(24.3 %) | 6<br>(16.2 %) | 6<br>(16.2 %) |
| Controls (n = 105) | 102<br>(97.1 %) | 1<br>(0.9 %) | 2<br>(1.9 %) | 0<br>- |

* $P < 0.001$

# Bleeding risk at delivery: epidemiology

- Discrepant results, depending on the severity of phenotype at baseline and the type of ascertainment; risk ranging from:
  - No increase[1]
  - Mild increase[2]
  - 7-10 fold higher (for patients unresponsive to desmopressin[3] or intermediate cases[4])

1. MCMDM-1VWD Study;
2. James and Jamison, JTH 2007
3. Foster, Thromb Haemost 1995
4. IMS, JTH 2005

# Classification of von Willebrand disease

## Quantitative deficiency

- *Type 1*: partial quantitative deficiency (~ 60-70 % of cases)
- *Type 3*: virtual absence (~ 1-2 % of cases)

## Qualitative deficiency

- *Type 2*: dysfunctional VWF (~ 25-30 % of cases)

  - A: loss of high molecular weight multimers
  - B: increased affinity for platelet Gp Ib
  - M: normal multimers with low activity
  - N: reduced VWF-FVIII binding

**VWD is a very heterogeneous bleeding disorder**
**Bleeding severity increases from type 1 to 3**
**and treatment differs**

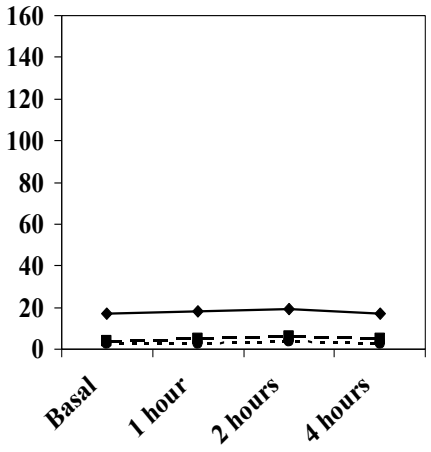
# The response to desmopressin trial as a turning point in VWD management

- Who:
  - All intermediate/severe cases
- Who not:
  - Severe homozygous (VWF:Ag < 3 IU/dL)
  - Enhanced responsiveness to RIPA (Type 2B)
  - Mild (VWF:RCo > 30 IU/dL)
- How:
  - IV or SC injections (0.3 μg/kg) or intranasal (150 - 300 μg)
  - Monitor FVIII, VWF:RCo at least after 1 and 4 hours
- Response criteria (FVIII and VWF:RCo):
  - Between 30 - 50 IU/dL, partial response
  - ≥ 50 IU/dL, complete response
  - In type 2N half-life of released FVIII:C may be short and VWF:FVIII products could be required

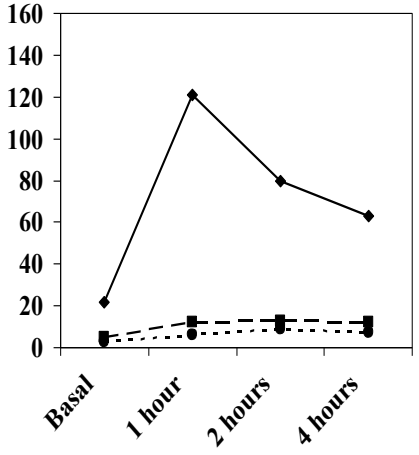
# DDAVP RESPONSE ACCORDING TO VWF MUTATIONS

◆ FVIII:C ; ■VWF:Ag ; •VWF:RCo (IU/dL)

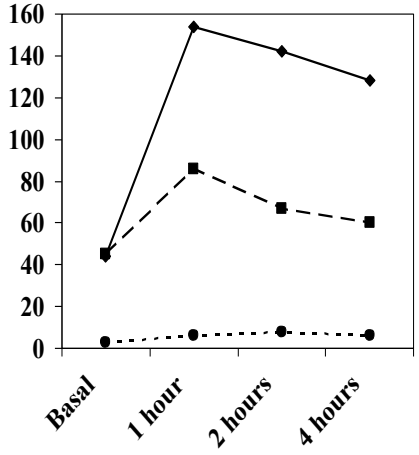
C2671Y/Deletion



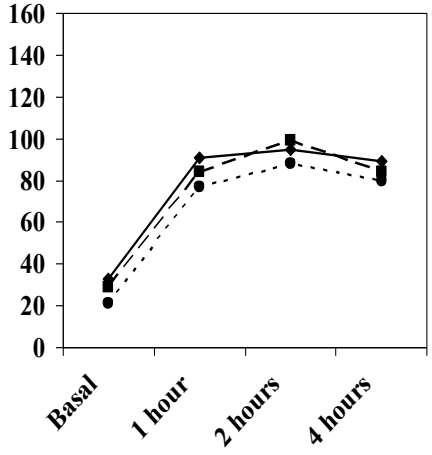

c.1534-3C>A IVS13/ Q77X



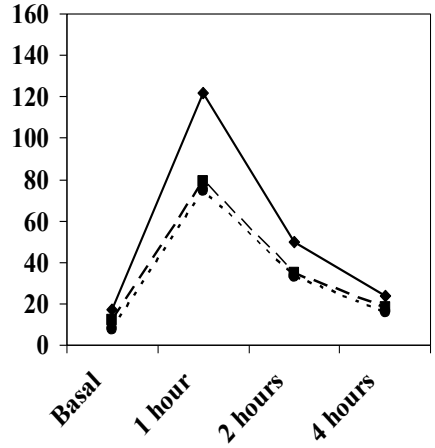

V1665E Type 2 A



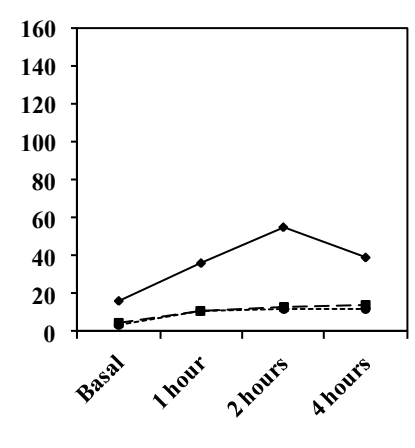

V1822G Type 1



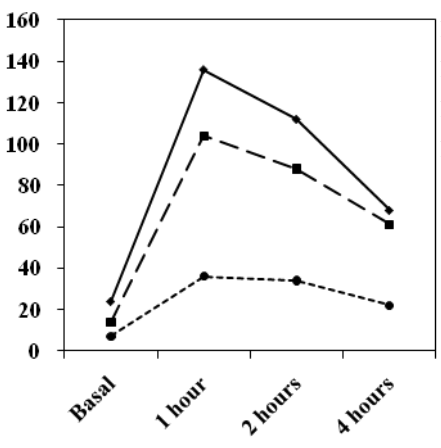

R1205H Type 1



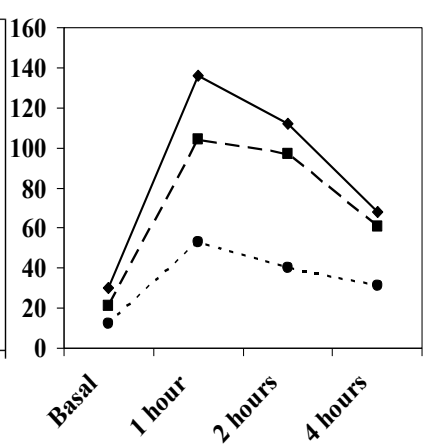

c.1534-3C>A IVS13/ C2362F




C1315L Type 2 M



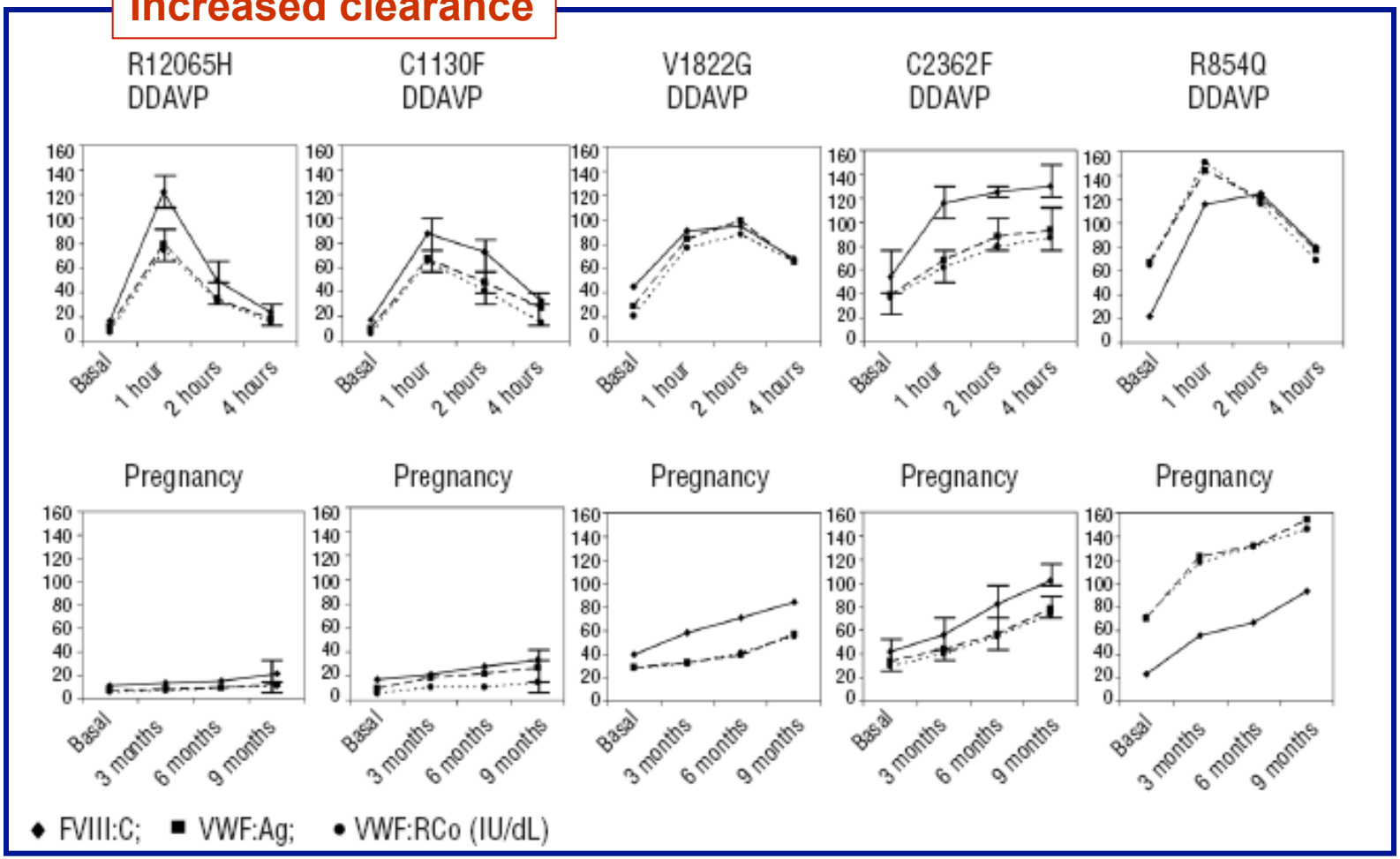

R1374H Type 2 A/M



# Pregnancy and delivery in women with von Willebrand's disease and different von Willebrand factor mutations

Giancarlo Castaman, Alberto Tosetto, and Francesco Rodeghiero

**Increased clearance**



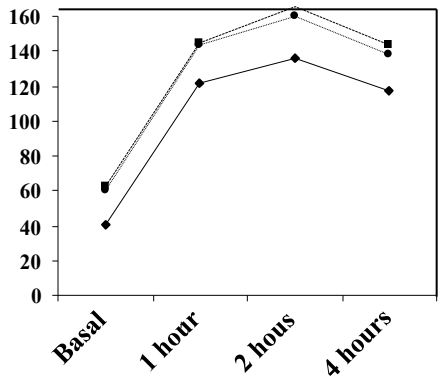

Haematologica, 2010

# Heterogeneity in type 2 N von Willebrand disease

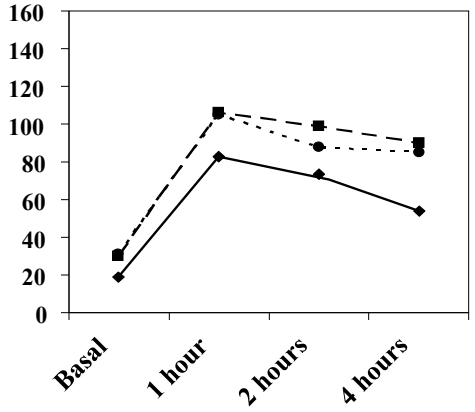
(Castaman 2005, 2010 and unpublished)

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

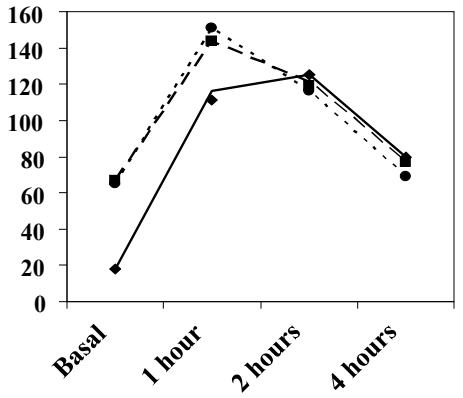
## R854Q Hetero DDAVP



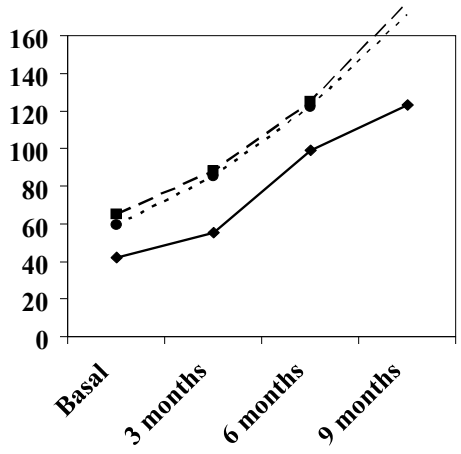

## R854Q/ c.1109+2T>C DDAVP



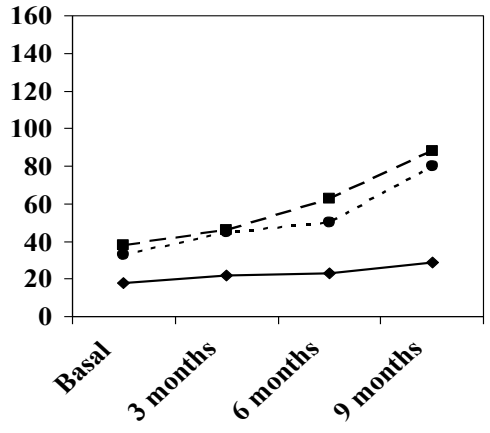

## R854Q HOMO DDAVP



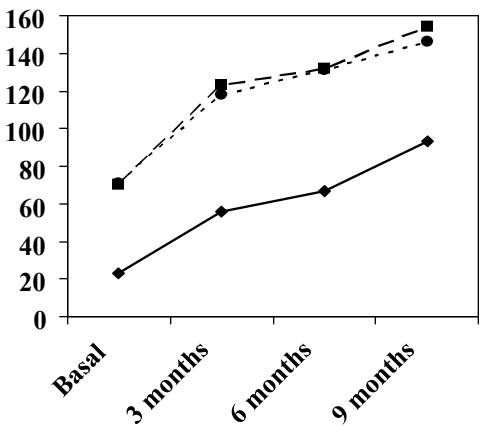

## Pregnancy




## Pregnancy




## Pregnancy




DDAVP at delivery

NO

YES

NO

# Desmopressin in Hemophilia A carriers and VWD women during early pregnancy

- 27 HA carriers + 5 VWD type 1 (FVIII:C 10 – 35 U/dL)
- 20 chorionic villus sampling at gestational weeks 11 to 12
  12 amniocentesis at gestational weeks 16 to 18
- Single infusion (22 cases); 2-3^ dose 18-24 hr apart in 10 cases
- Median FVIII:C 60 min post-infusion (60 U/dL, range 40 – 121), 3-fold median increase
- No bleeding complications; no miscarriages

Mannucci, Blood 2005; 105: 3382

# Desmopressin in VWD during late pregnancy

- 54 women: 5 in 1st trimester, 30 before vaginal and 45 before cesarean delivery (Sànchez-Luceros et al, Thromb Res 2007)

- In our practice, desmopressin immediately after umbilical cord clamping for vaginal delivery (>120 cases)

- No fluid retention, no oxytocin-like effect, no miscarriage

# Women with VWD, pregnancy and delivery (I)

- Uterine bleeding risk limited especially to severe cases
- Lab monitoring during pregnancy always advised (at least 1-2 months before delivery)
- FVIII/VWF usually normalize at the end of pregnancy when basal levels are > 30 U/dL (Conti et al 1984; Kadir et al, 1999; Castaman et al, 2010)
- Levels FVIII and VWF> 50 U/dL usually safe to avoid anti-hemorrhagic prophylaxis (including epidural anaesthesia)

# Women with VWD, pregnancy and delivery (II)

- Women carrying peculiar, frequent mutations (R1205H, C1130F, R1374H), type 3 and some type 2 do not show significant improvement during pregnancy (Castaman et al, 2001; 2006; 2010)

- Desmopressin immediately after umbilical cord clamping and 12 - 24 and 48 hours after is advisable, depending also on the requirement for episiotomy

- Replacement therapy in unresponsive patients (~ 50 U/kg at delivery, 20-40 U/kg as needed to cover at least 5-7 days). Lab monitoring advisable

# Women with VWD, pregnancy and delivery (III)

- Avoid traumatic devices at partum for risk of hematoma in the newborn
- Quantitative estimation of blood losses desirable
- Cesarean section only for obstetric reasons
- Blood sampling for the neonate not required, unless a potential type 3 VWD offspring is expected

# Women with type 2B VWD in pregnancy and at delivery

- Drop of platelet count (nadir ~ 50,000/μL) with some mutations (e.g., R1306W, R1308C) because of the increase of abnormal VWF with enhanced affinity for GpIbα on platelet membrane (Rick 1987; Federici 2009)

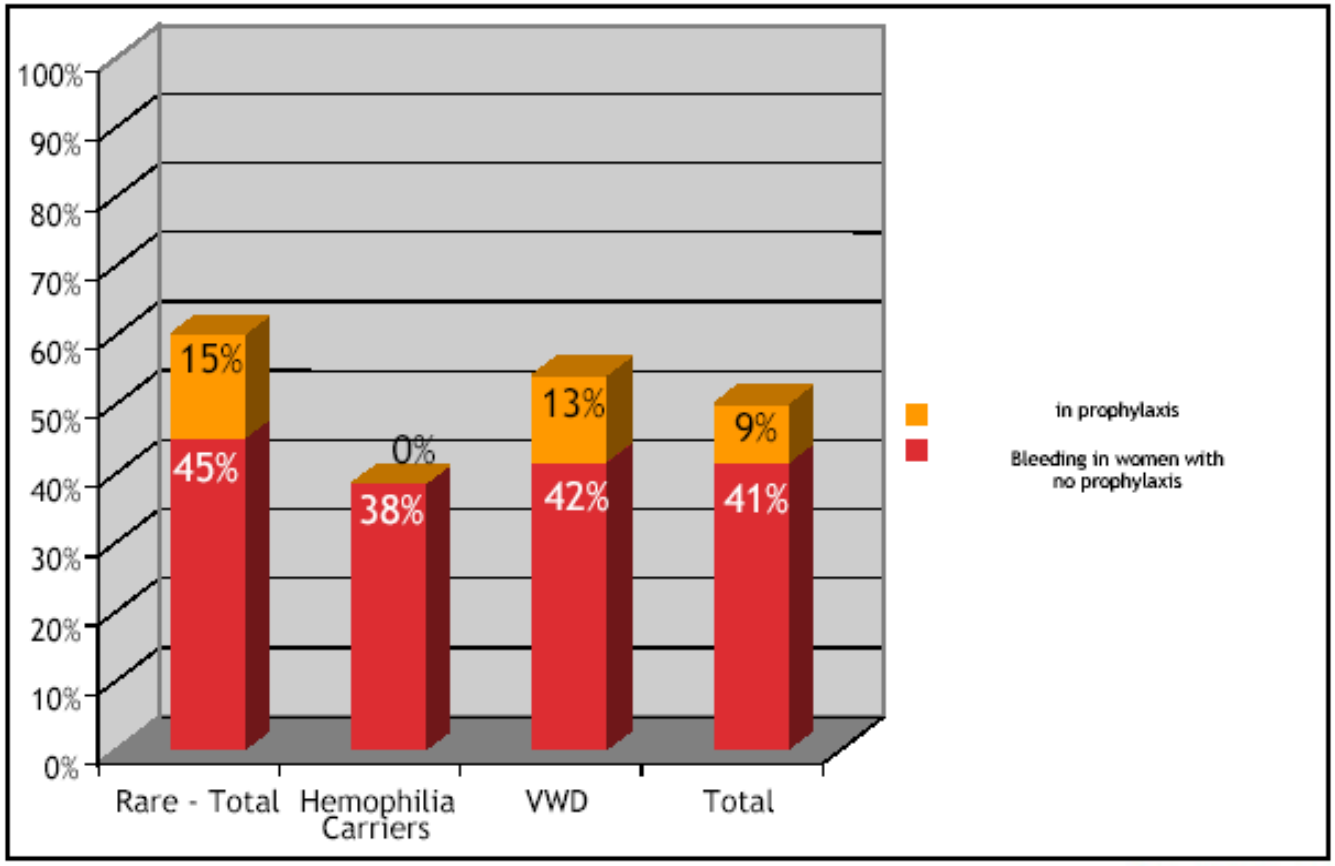
- Platelet transfusion used at delivery in some cases, along with VWF/FVIII concentrates (Mathew 2003)

- No significant changes and no treatment required for P1266Q/L (frequent in Italy) (Castaman and Federici, unpublished)

# Risk of delayed post-partum bleeding in women with VWD

- An average risk of 25 % > 24 h-2-3 weeks following delivery (Ramsahoye 1995; Kadir 1998)
- VWF returns to baseline within 7-10 days
- Prolonged treatment for type 2 and type 3 at delivery
- Oral antifibrinolytics in case of excessive bleeding

# Frequency of post-partum bleeding in 64 women




HEMOPHILIA MANAGEMENT & AWARENESS

Siboni et al, Haemophilia 2009

# Conclusions

- Pregnancy in mild VWD women is almost uneventful and treatment seldom required
- Women with VIII/VWF level < 30 U/dL at baseline must be checked at least 1-2 months prior to delivery to plan appropriate treatment at partum
- DDAVP-responsive women and VIII/VWF level < 50 U/dL can be managed safely with the compound
- DDAVP-unresponsive women must be treated with VWF/FVIII concentrates
- For delivery, a multidisciplinary approach is advisable and appropriate management supervised by an expert in Coagulation disorders

# Managing Type 3 VWD with FVIII derived VWF containing concentrate at time of delivery

- Dosing at delivery typically has been 40-80 IU/kg.
- Post-partum prophylaxis typically has been 20-40 IU/kg of a plasma-derived VWF containing concentrate {Foster, 1995} for at least one-week partum ideally tapered over the 4 week post-partum period.{Caliezi, 1998}
  - Treatment beyond 1 week has been advised as post-partum hemorrhage has been reported for up to 4 weeks especially if treatment is for only 1 week post-partum {Conti, 1986;Lak, 2000}.
- Consequently, an area worthy of further study is to determine the optimal :
  a) duration
  b) schedule of infusional therapy post-partum based on present patterns of care.

HEMOPHILIA
MANAGEMENT & AWARENESS

# Type 2,3 VWD: Obstetrical issues

- Definite increased risk of post-partum hemorrhage in Type 2 and 3 VWD compared to the baseline 2-5% risk in the normal pregnant population as recently summarized by Kujovich, JTH 2005:

| Haemorrhage type | % of all deliveries | % women with VWD |
|---|---|---|
| Primary* | 16–29 | 23–43 |
| Secondary† | 20–29 | 29–43 |
| Overall‡ | 38–50 | 34–71 |
| VWD Subtype§ | | |
| Type 1 | 10–37 | 16–42 |
| Type 2 | 50–54 | 18–83 |
| Type 3 | 27 | 15–26 |

HEMOPHILIA MANAGEMENT & AWARENESS

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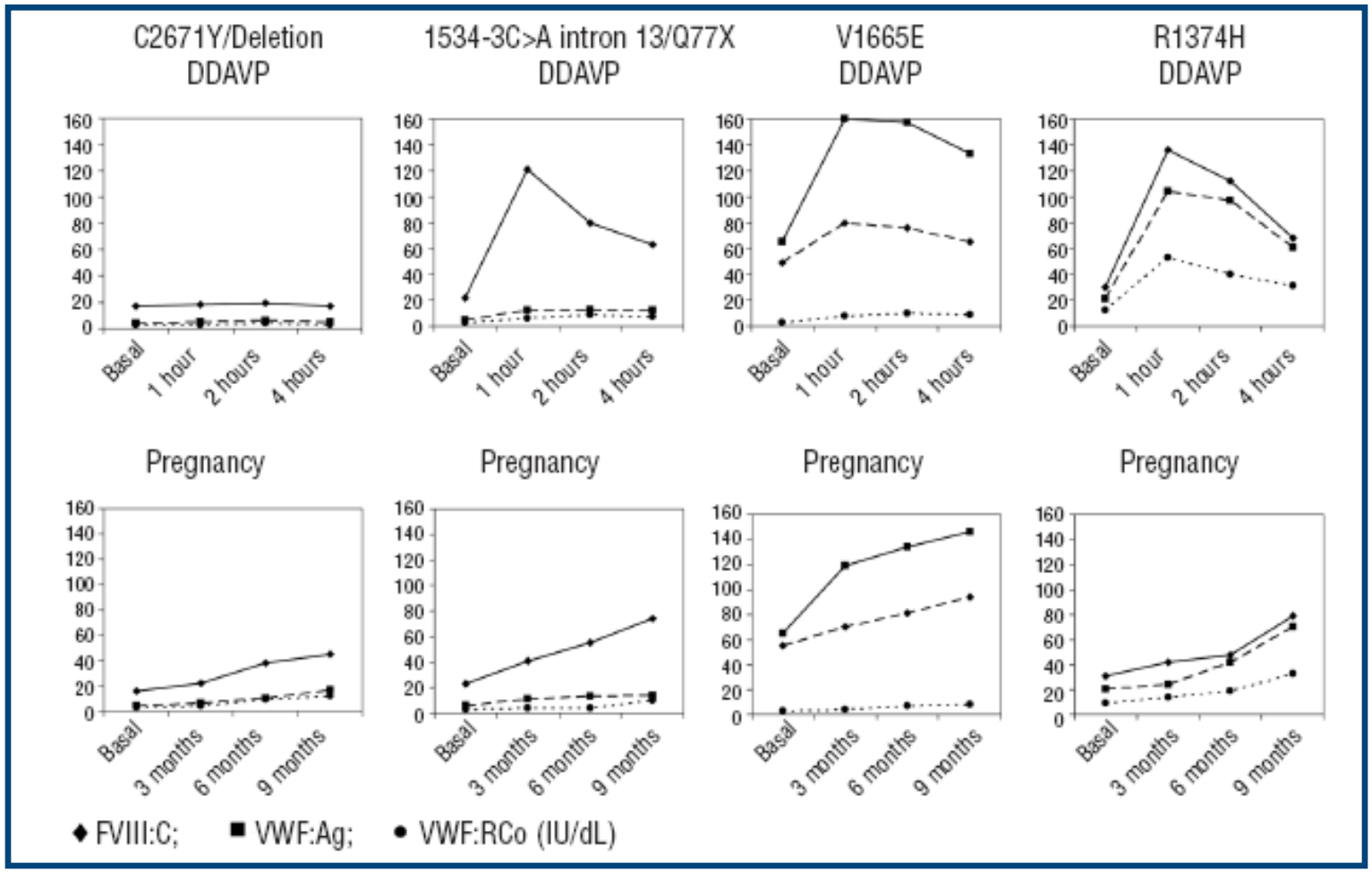


Haematologica, 2010