dr. rott
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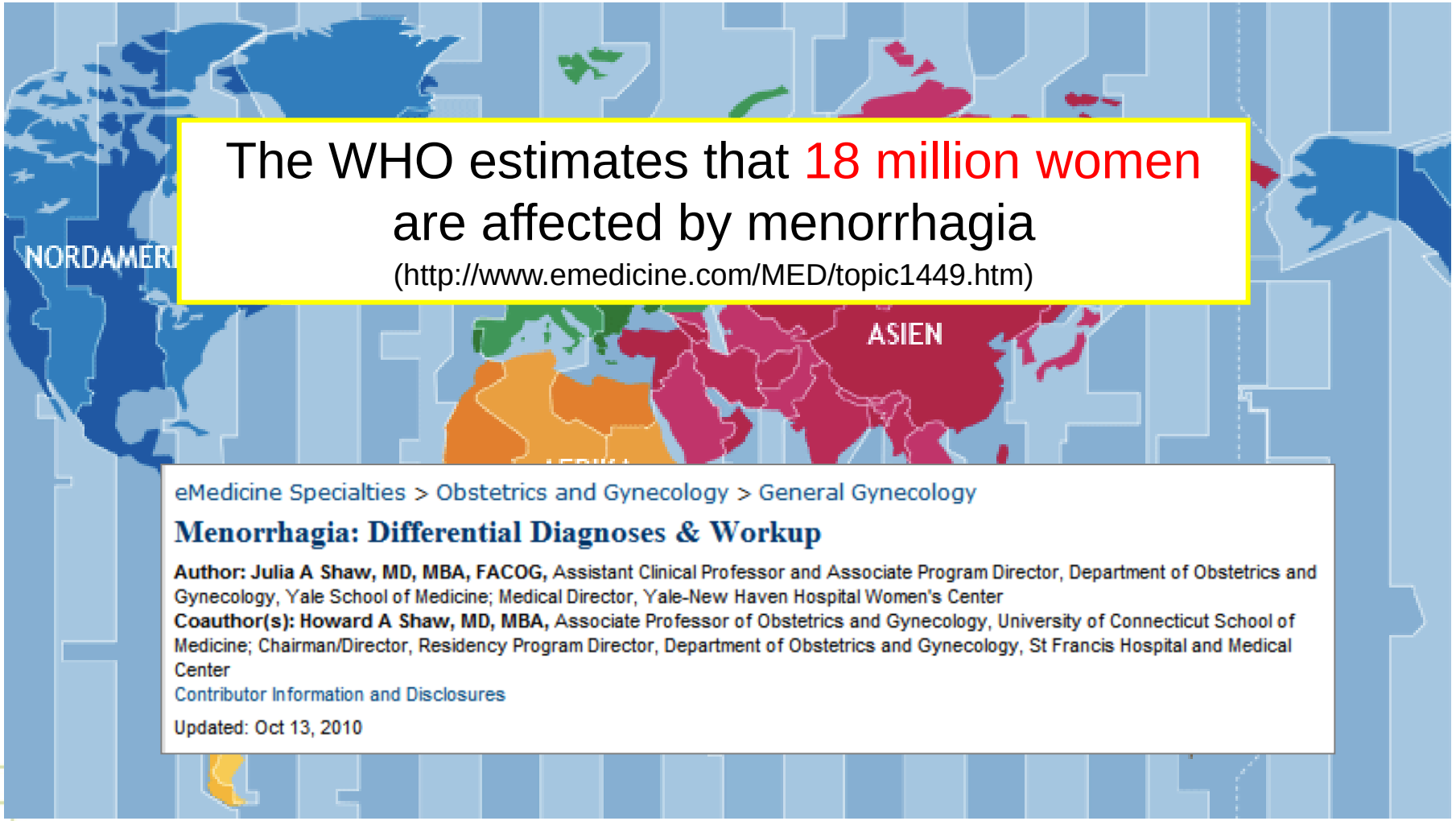
gerinnungs
zentrum
rhein-ruhr

# Bleeding disorders in women

Dr. med. Susan Halimeh

The WHO estimates that 18 million women are affected by menorrhagia

(http://www.emedicine.com/MED/topic1449.htm)




eMedicine Specialties > Obstetrics and Gynecology > General Gynecology

**Menorrhagia: Differential Diagnoses & Workup**

**Author: Julia A Shaw, MD, MBA, FACOG,** Assistant Clinical Professor and Associate Program Director, Department of Obstetrics and Gynecology, Yale School of Medicine; Medical Director, Yale-New Haven Hospital Women's Center

**Coauthor(s): Howard A Shaw, MD, MBA,** Associate Professor of Obstetrics and Gynecology, University of Connecticut School of Medicine; Chairman/Director, Residency Program Director, Department of Obstetrics and Gynecology, St Francis Hospital and Medical Center

Contributor Information and Disclosures

Updated: Oct 13, 2010

# Historical use of terminolgies and definitions- The process of menstruation

- **„Bees will die and dogs tasting her blood run mad“**
- **„ should a menstruating woman sit under a tree, the fruit will fall“**

  (from Books VII and XXVIII of Pliny´s Historia Naturalis)

- **„the periodic uterine haemorrhage is in fact one of the sacrifices which women must offer at the altar of evolution and civilisation“**

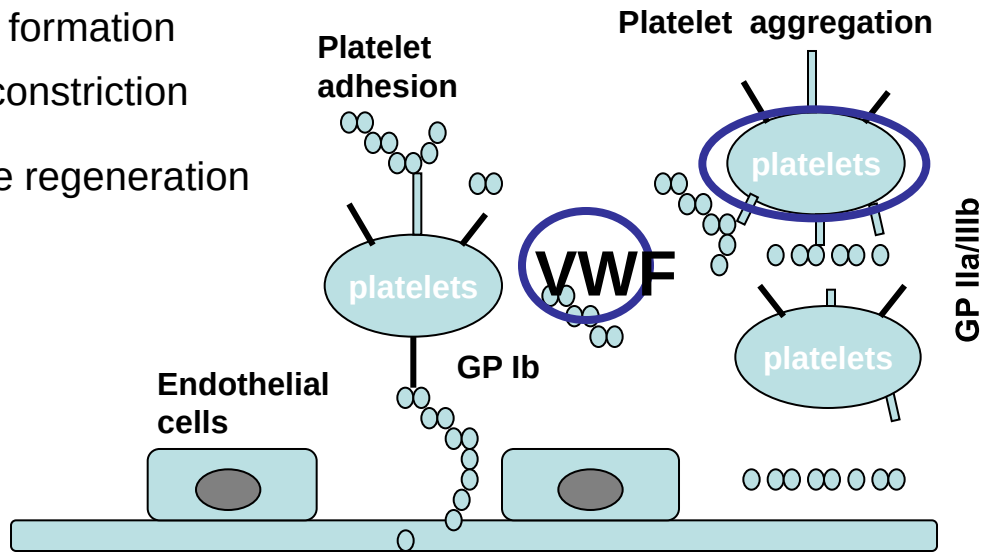
  (in modern times: H. Beckwith Whitehouse)

# Menstruation blood loss

**INADEQUATE INDUCTION** **and/or** **OVER-COMPENSATION**

- VWF mediated platelet aggregation
- Fibrin formation
- Vasoconstriction
- Tissue regeneration

- PG induced platelet inhibition
- Fibrinolysis
- Vasodilatation




Increased menstrual blood loss

MENORRHAGIA





Thank you to Rezan Kadir

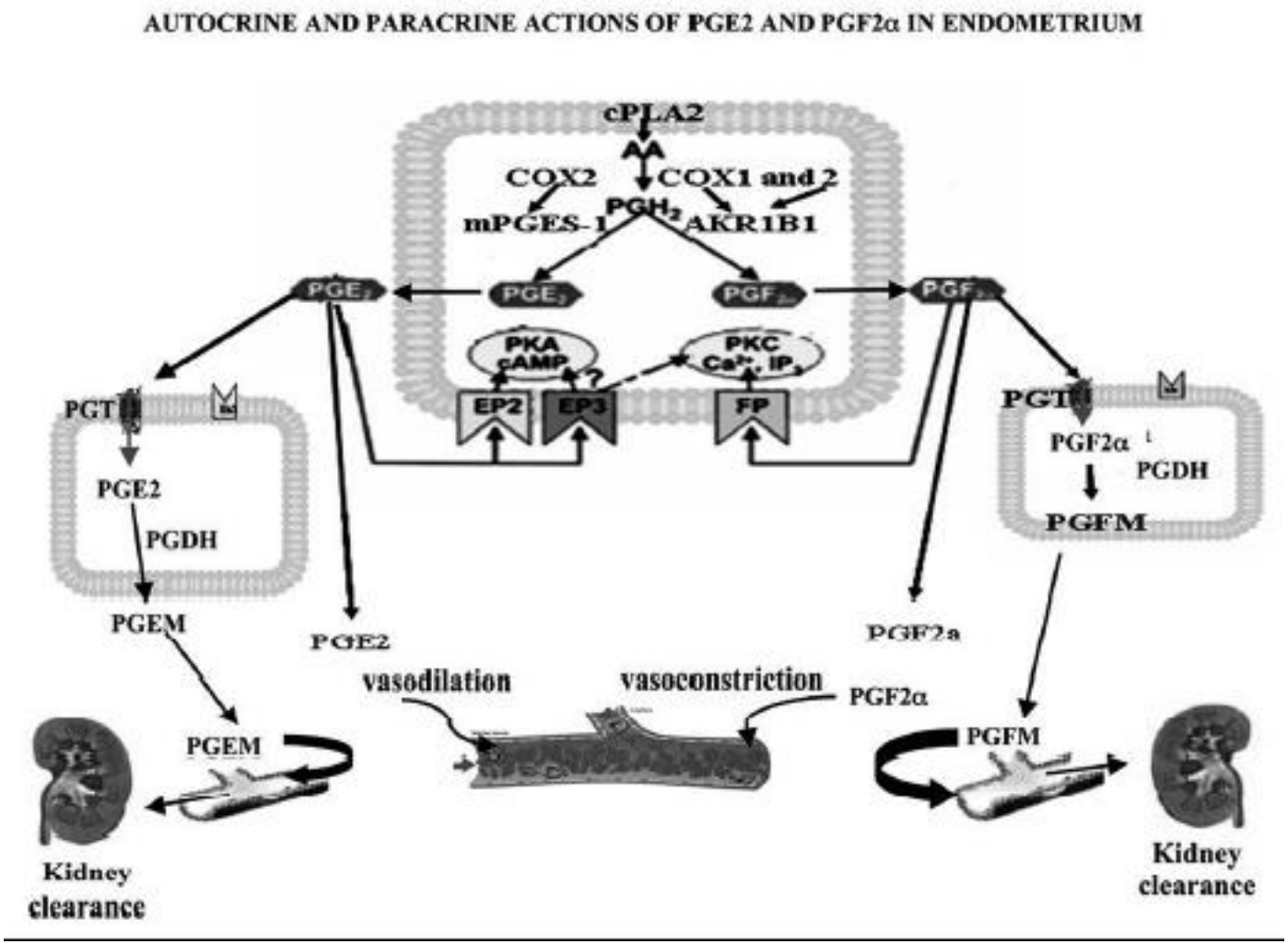
# Menarche

- Hallmark event
- Transformation from childhood to puberty
- Anovulatory cycles:➔ LH and FSH secretion is sufficient to induce follicular development and oestrogen production.. BUT inadequate to induce follicular maturation and ovulation.

# Menarche

- In proliferate phase the endometrium synthesizes amounts of PGF2 (vasoconstrictor and weak platlet aggreagator) and PGE2 (vasodilatator and weak platlet antiaggregator)
- In normal menstruation the Ratio of PGF2:PGE2 is 2:1
- ➔ in anovulatory **DUB the lack of progesterone** results in decreased PGF2➔ so there is a relative increase in vasodilatator PGE2➔ increasing the menstrual blood

# Mechanism of PGF2 and PGE2



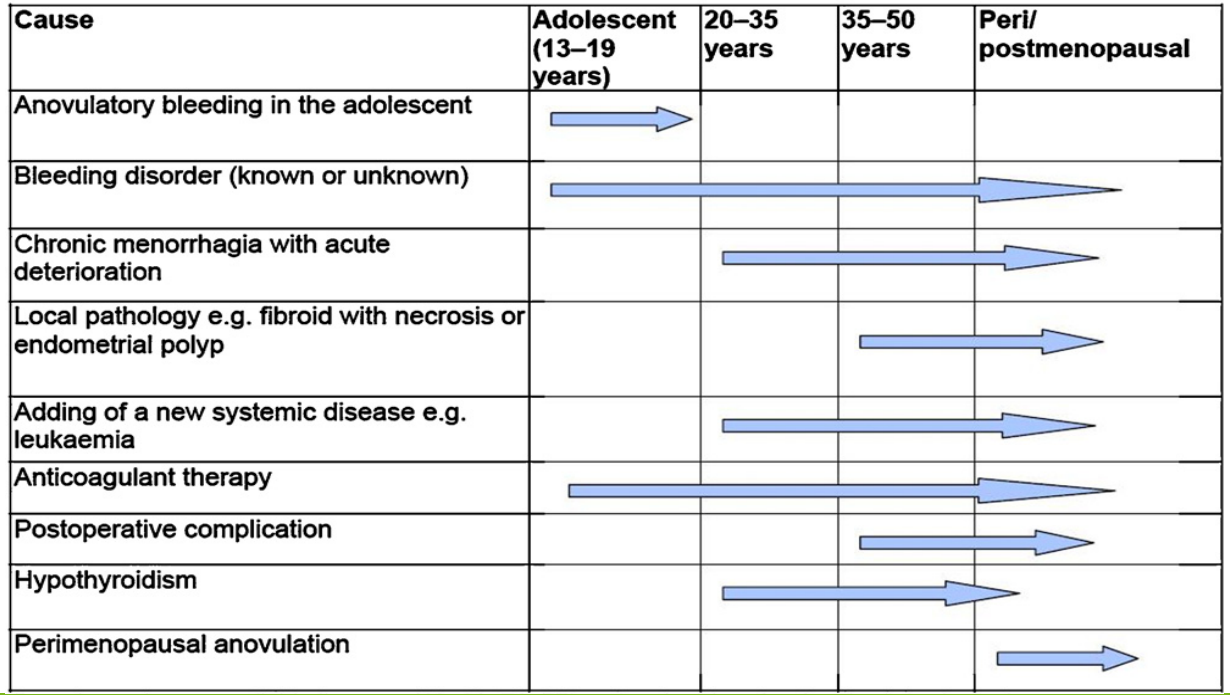
European Journal of Obstetrics & Gynecology and Reproductive Biology

2011

Review

# Evaluation and management of acute menorrhagia in women with and without underlying bleeding disorders: consensus from an international expert panel

Andra H. James [a,*], Peter A. Kouides [b], Rezan Abdul-Kadir [c], Jennifer E. Dietrich [d], Mans Edlund [e], Augusto B. Federici [f], Susan Halimeh [g], Pieter Willem Kamphuisen [h], Christine A. Lee [i], Oscar Martínez-Perez [j], Claire McLintock [k], Flora Peyvandi [l], Claire Philipp [m], Jeffrey Wilkinson [n], Rochelle Winikoff [o]



# Menorrhagia- Definition

Excessive or prolonged uterine bleeding that exceeds 80 mL of blood loss per menstruation (in the presence of a normal secretory endometrium after normal ovulation)

Valle RF and Sciarra JJ. In: Menorrhagia. Oxford: Isis Medical Media, 1999

**Normal** menstrual cycle

25–35 days in duration, with bleeding lasting an average of 5 days and total blood flow between 25 and 80 mL

**Menorrhagia**

A blood loss of greater than 80 ml per menstrual cycle or lasting longer than 7 days

Lentz GM, Abnormal Uterine Bleeding. In Katz VL, Lentz GM Comprehensive Gynecology5Th 2007; 915-932

# Definition of Menorrhagia



- **Heavy menstrual bleeding since menarche**
- **One of the following conditions:**
  - Postpartum hemorrhage
  - Surgery- related bleeding
  - Bleeding associated with dental work
- **Two or more of the following conditions:**
  - Bruising, one to two times per month
  - Epistaxis, one to two times per month
  - Frequent gum bleeding
  - Family history of bleeding symptoms

Modified from Kouides PA, Conrad J, Peyvandi F, Lukes A, Kadir R. Fertil Steril 2005; 84: 1345-51

# Etiologies of acute abnormal uterine bleeding

**Abnormal uterine bleeding:**

Heavy menstrual bleeding (AUB/HMB)

Intermenstrual bleeding (AUB/IMB)

## PALM-structure causes:

**P**olyp (AUB-A)
**A**denomyosis (AUB-A)
**L**eimyoma (AUB-L)
**M**alignanacy and hyperplasia (AUB-M)

## COEIN-nonstructure causes:

**C**oagulopathy (AUB-C)
**O**vulatory dysfunction (AUB-O)
**E**ndometrial (AUB-E)
**I**atrogenic (AUB-I)
**N**ot yet classified (AUB-N)

FIGO Working Group on Mentrual disorders. Int J Gynaecol Obstet 2011; 113:3-13

# Women with bleeding disorders- Menorrhagia

Iron deficiency anaemia

64% in women with bleeding disorders Vs 34% control

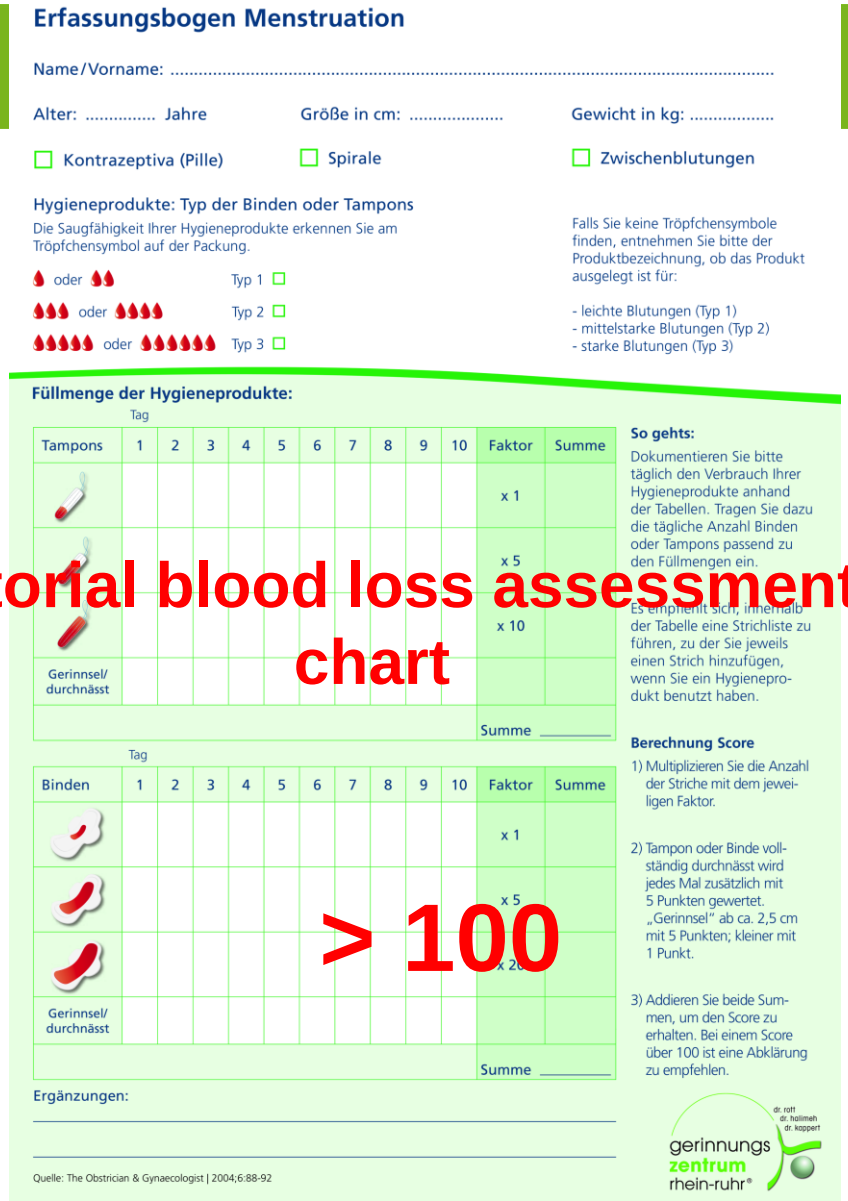
Kadir et al 1999, Kouides et al 2000

FBC and Ferritin assessment

Predictors for underlying bleeding disorders

Clinical anaemia – odd ratio 3.3
Low ferritin - predict 60% of MBL>80ml
-Odd ratio 51 for Iron deficiency anaemia

Jayasinghe et al 2005, Warner et al 2004



## Erfassungsbogen Menstruation

Name/Vorname: .....

Alter: ..... Jahre  Größe in cm: .....  Gewicht in kg: .....

☐ Kontrazeptiva (Pille)  ☐ Spirale  ☐ Zwischenblutungen

**Hygieneprodukte: Typ der Binden oder Tampons**

Die Saugfähigkeit Ihrer Hygieneprodukte erkennen Sie am Tröpfchensymbol auf der Packung.

oder Typ 1 ☐

oder Typ 2 ☐

oder Typ 3 ☐

Falls Sie keine Tröpfchensymbole finden, entnehmen Sie bitte der Produktbezeichnung, ob das Produkt ausgelegt ist für:

- leichte Blutungen (Typ 1)
- mittelstarke Blutungen (Typ 2)
- starke Blutungen (Typ 3)

**Füllmenge der Hygieneprodukte:**

Tag

| Tampons | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Faktor | Summe |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | x 1 | |
| | | | | | | | | | | | x 5 | |
| | | | | | | | | | | | x 10 | |
| Gerinnsel/ durchnässt | | | | | | | | | | | | |
| | | | | | | | | | | | Summe | |

Tag

| Binden | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Faktor | Summe |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | x 1 | |
| | | | | | | | | | | | x 5 | |
| | | | | | | | | | | | x 20 | |
| Gerinnsel/ durchnässt | | | | | | | | | | | | |
| | | | | | | | | | | | Summe | |

**So gehts:**

Dokumentieren Sie bitte täglich den Verbrauch Ihrer Hygieneprodukte anhand der Tabellen. Tragen Sie dazu die tägliche Anzahl Binden oder Tampons passend zu den Füllmengen ein.

Es empfiehlt sich, innerhalb der Tabelle eine Strichliste zu führen, zu der Sie jeweils einen Strich hinzufügen, wenn Sie ein Hygieneprodukt benutzt haben.

**Berechnung Score**

1) Multiplizieren Sie die Anzahl der Striche mit dem jeweiligen Faktor.

2) Tampon oder Binde vollständig durchnässt wird jedes Mal zusätzlich mit 5 Punkten gewertet. „Gerinnsel" ab ca. 2,5 cm mit 5 Punkten; kleiner mit 1 Punkt.

3) Addieren Sie beide Summen, um den Score zu erhalten. Bei einem Score über 100 ist eine Abklärung zu empfehlen.

Ergänzungen:

Quelle: The Obstrician & Gynaecologist | 2004;6:88-92

gerinnungszentrum rhein-ruhr®

**Pictorial blood loss assessment chart**

**> 100**

# 96% sensitivity increasing

Higham JM et al. Assessment of menstrual blood loss using a pictorial chart. Br. J Obstet Gynecol 1990; 97: 737-9

# Age and the Prevalence of Bleeding Disorders in Women With Menorrhagia

Claire S. Philipp, MD, Ambarina Faiz, MD, MPH, Nicole Dowling, PhD, Anne Dilley, PhD,*
Lisa A. Michaels, MD, Charletta Ayers, MD, MPH, Connie H. Miller, PhD, Gloria Bachmann, MD,
Bruce Evatt, MD, and Parvin Saidi, MD

VOL. 105, NO. 1, JANUARY 2005
© 2005 by The American College of Obstetricians and Gynecologists.
Published by Lippincott Williams & Wilkins.

**Table 1.** Characteristics of Women With Menorrhagia

| Characteristic | Number of Patients | Age Group (yr) ≤ 19 (n = 25) | 20–44 (n = 65) | ≥ 45 (n = 25) | *P* |
|---|---|---|---|---|---|
| Age at menarche (y) | 101* | 12.6 ± 1.5 (24) | 12.2 ± 1.7 (57) | 11.9 ± 1.4 (20) | .28 |
| Duration of menses (d) | 111* | 7.7 ± 2.1 (22) | 7.8 ± 3.4 (65) | 6.7 ± 2.1 (24) | .28 |
| Length of cycle (d) | 91* | 26 ± 7.6 (14) | 27 ± 5.7 (53) | 26 ± 4.3 (24) | .58 |
| Race [no. (%)] | 115 | | | | .20 |
| White | 79 | 20 (80) | 41 (63) | 18 (72) | |
| Black | 25 | 3 (12) | 15 (23) | 7 (28) | |
| Other | 11 | 2 (8) | 9 (14) | 0 | |
| Blood group [no. (%)] | 115 | | | | .50 |
| O | 60 | 11 (44) | 37 (57) | 12 (48) | |
| Non-O | 55 | 14 (56) | 28 (43) | 13 (52) | |
| Hemoglobin (g/dL) | 115 | 12.5 ± 1.3 (10.7–15.4) | 11.7 ± 2 (4.3–14.5) | 11.6 ± 1.9 (6–13.8) | .13 |
| Anemia† [n (%)] | 115 | 9 (36) | 28 (43) | 10 (40) | .82 |
| Platelet count ($\mu L^{-1}$) | 115 | 262.1 ± 76 (103–460) | 284.3 ± 71 (102–449) | 290.5 ± 72 (177–430) | .32 |

Data for age groups are presented as mean ± standard deviation (n), mean + standard deviation (range), or n (%), as indicated.
* Study subjects with known information.
† Hemoglobin less than 12 g/dL.

Acta Obstetricia et Gynecologica
2009, 1–5, iFirst article

ORIGINAL ARTICLE

# Quantification of menstrual flow by weighing protective pads in women with normal, decreased or increased menstruation

BRYNJA R. GUDMUNDSDOTTIR[1,5], ELIN F. HJALTALIN[2], GUDRUN BRAGADOTTIR[1], ARNAR HAUKSSON[3], REYNIR T. GEIRSSON[4,5] & PALL T. ONUNDARSON[1,5]

[1]Department of Laboratory Hematology and Hemostasis Center, Landspitali University Hospital, Hringbraut, Reykjavik 101, Iceland, [2]Primary Healthcare, Efra Breidholt, Reykjavik 109, Iceland, [3]Maternity Center, Reykjavik 101, Iceland, [4]Department of Obstetrics and Gynecology, Landspitali University Hospital, Reykjavik 101, Iceland and [5]School of Medicine, University of Iceland, Laeknagardur, Vatnsmyri, Reykjavik, Iceland

# Length of menstruation period

Table I. Characteristics of menstruation in the study groups*.

| | Healthy adult women | Healthy teenage girls | Healthy adults and teenage girls | Healthy on OCP | Untreated menorrhagic women | Menorrhagic women on OCP | Teenage girls claiming heavy menses |
|---|---|---|---|---|---|---|---|
| Number | 26 | 52 | 78 | 7 | 17 | 5 | 6 |
| Age | 35 (37; 24–46) | 17 (16; 16–18) | 23 (17; 16–46) | 24 (26; 16-28) | 39 (38; 31–49) | 30 (29; 16–45) | 16 (16; 16–16) |
| Measured menstruation length (days) | 5 (5; 3–8) | 5 (6; 3–7) | 5 (5; 3–8) | 4 (4; 2–5) | 7 (6; 4–12) | 5 (5; 4–7) | 6 (6; 5–8) |
| Protective pad number | 13 (16; 4–27) | 14 (13; 5–33) | 14 (13; 4–33) | 8 (8; 5–12) | 26 (24; 12–44) | 13 (14; 9–16) | 15 (13; 8–25) |
| History of diagnosed iron deficiency | 3/26 | 4/52 | 7/78 | 2/7 | 14/17 | 4/5 | 3/6 |

*Results are shown as mean (median; range).

Brynja R. Gudmundsdottir et al. Quantification of menstrual flow by weighing protctive pads in women with normal, decreased or increased mentruation Acta Obstrtricia et Gynecologica 2009, 1-5

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Haemophilia

*Haemophilia* (2011), **17** (Suppl. 1), 6–13 DOI: 10.1111/j.1365-2516.2011.02558.x

ORIGINAL ARTICLE

# Surveillance of female patients with inherited bleeding disorders in United States Haemophilia Treatment Centres

V. R. BYAMS,* P. A. KOUIDES,† R. KULKARNI,‡ J. R. BAKER,§ D. L. BROWN,¶ J. C. GILL,** A. M. GRANT,* A. H. JAMES,†† B. A. KONKLE,‡‡ J. MAAHS,§§ M. M. DUMAS,¶¶ S. McALISTER,* D. NANCE,‡‡ D. NUGENT,*** C. S. PHILIPP,††† J. M. SOUCIE* and E. STANG,‡‡‡ and the Haemophilia Treatment Centres Network Investigators

**Table 3.** Frequency of bleeding symptoms and provider intervention ($n$ = 319).

| | $n$ (%) reported symptom | $n$ (%) required provider intervention |
|---|---|---|
| More than one nosebleed per year lasting 10 min or longer | 154 (48.4) | 75 (48.7) |
| Oral mucosal bleeding lasting 10 min or longer | 93 (29.4) | 43 (46.2) |
| Bleeding during or after dental procedures of concern to healthcare provider | 111 (35.1) | 73 (65.8) |
| Bleeding from minor cuts lasting 5 min or longer | 153 (48.0) | 23 (15.0) |
| Bruises larger than a quarter size occurring at least once a month without trauma | 174 (54.5) | 13 (7.5) |
| Bleeding after surgery of concern to health care provider | 119 (37.3) | 102 (85.7) |
| Menstrual bleeding that required protection change at least every 2 h on heaviest day* | 165 (76.0) | 95 (57.6) |
| Bleeding during pregnancy and/or postpartum of concern to health care provider† | 63 (52.9) | 51 (81.0) |
| Joint bleeding | 51 (16.0) | 37 (72.5) |
| Muscle bleeding | 28 (8.8) | 13 (46.4) |
| CNS bleeding | 9 (2.8) | 7 (77.8) |
| GI bleeding | 37 (11.6) | 23 (62.6) |

Haemophilia

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| Bruises larger than a dime on joints occurring at least once a month without trauma | 174 (54.5) | 13 (7.5) |
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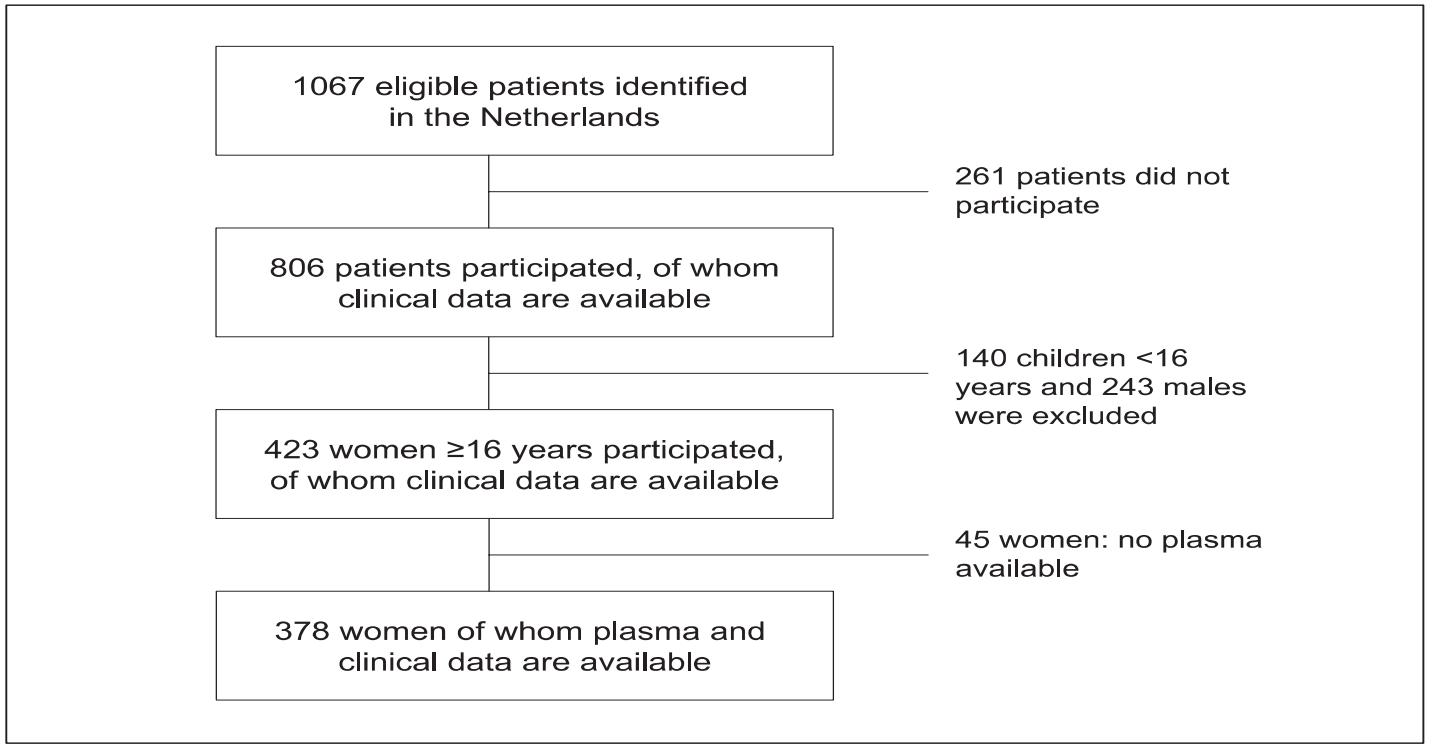
**Menstrual bleeding that required protection change at least every 2h 165 (76%)**

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# Gynaecological and obstetric bleeding in moderate and severe von Willebrand disease

**Eva M. de Wee[1]; H. Marieke Knol[2,3]; Eveline P. Mauser-Bunschoten[4]; Johanna G. van der Bom[5,6]; Jeroen C. J. Eikenboom[5,7]; Karin Fijnvandraat[8]; Arja de Goede-Bolder[9]; Britta Laros-van Gorkom[10]; Paula F. Ypma[11]; Sonja Zweegman[12]; Karina Meijer[2]; Frank W. G. Leebeek[1]; for the WiN study group**

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gerinnungszentrum rhein-ruhr
dr. rott
dr. halimeh
dr. kappert

**Table 3: Menorrhagia in women with moderate or severe VWD.**

| | | Total (n=423) | | Type 1 (n=242) | | Type 2 (n=120) | | Type 3 (n=16) | | P-value* |
|---|---|---|---|---|---|---|---|---|---|---|
| Age of menarche | median, IQR | 13 | 12–14 | 13 | 12–14 | 13 | 12–14 | 13 | 12–14 | 0.63 |
| Duration period | median, IQR | 7 | 6–8 | 7 | 6–8 | 7 | 6–8 | 7 | 7–10 | 0.76 |
| Number of days heavy menstrual bleeding | median, IQR | 4 | 3–5 | 4 | 3–6 | 4 | 3–5 | 4 | 3–6.5 | 0.41 |
| Menorrhagia symptoms | median, IQR | 3 | 2–4 | 3 | 2–4 | 3 | 2–4 | 3 | 1–4 | 0.52 |
| Excessive menstrual bleeding | n, % | 347 | 82% | 202 | 83% | 98 | 82% | 13 | 81% | 0.19 |
| Loss of blood clots | n, % | 338 | 80% | 196 | 81% | 100 | 83% | 10 | 63% | 0.48 |
| Requirement of iron or blood transfusion | n, % | 184 | 44% | 105 | 43% | 60 | 50% | 10 | 63% | 0.08 |
| Heavy menstrual flow that interferes with daily life | n, % | 192 | 45% | 110 | 45% | 58 | 48% | 7 | 44% | 0.77 |
| Menstrual period that lasts > 7 days | n, % | 150 | 36% | 81 | 33% | 51 | 43% | 6 | 38% | 0.16 |
| Menorrhagia ≥2 symptoms present | n, % | 342 | 81% | 196 | 81% | 99 | 83% | 12 | 75% | 0.76 |
| Menorrhagia severity | median, IQR | 3 | 2–4 | 3 | 2–4 | 3 | 2–4 | 3 | 2–4 | 0.10 |
| 0: no menorrhagia | n, % | 64 | 15% | 41 | 17% | 13 | 11% | 1 | 6% | |
| 1: consultation only | n, % | 29 | 7% | 19 | 8% | 5 | 4% | 1 | 6% | |
| 2: antifibrinolytics or pill use | n, % | 98 | 23% | 46 | 19% | 31 | 26% | 5 | 31% | |
| 3: dilatation and currettage or iron therapy | n, % | 121 | 29% | 74 | 31% | 37 | 31% | 3 | 19% | |
| 4: blood transfusion, FVIII/VWF concentrate, desmopressin or hysterectomy | n, % | 111 | 26% | 62 | 26% | 34 | 28% | 9 | 56% | |

* Chi square or ANOVA test for differences between subgroups. IQR, interquartile range.

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# Gynaecological and obstetric bleeding in moderate and severe von Willebrand disease

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| Age of menarche | median, IQR | 13 | 12–14 | 13 | 12–14 | 13 | 12–14 | 13 | 12–14 | 0.63 |
| Duration period | median, IQR | 7 | 6–8 | 7 | 6–8 | 7 | 6–8 | 7 | 7–10 | 0.76 |
| Number of days heavy menstrual bleeding | median, IQR | 4 | 3–5 | 4 | 3–6 | 4 | 3–5 | 4 | 3–6.5 | 0.41 |
| Menorrhagia symptoms | median, IQR | 3 | 2–4 | 3 | 2–4 | 3 | 2–4 | 3 | 1–4 | 0.52 |
| Excessive menstrual bleeding | n, % | 347 | 82% | 202 | 83% | 98 | 82% | 13 | 81% | 0.19 |
| Loss of blood clots | n, % | 338 | 80% | 196 | 81% | 100 | 83% | 10 | 63% | 0.48 |
| Requirement of iron or blood transfusion | n, % | 184 | 44% | 105 | 43% | 60 | 50% | 10 | 63% | 0.08 |
| Heavy menstrual flow that interferes with daily life | n, % | 192 | 45% | 110 | 45% | 58 | 48% | 7 | 44% | 0.77 |
| Menstrual period that lasts > 7 days | n, % | 150 | 36% | 81 | 33% | 51 | 43% | 6 | 38% | 0.16 |
| Menorrhagia ≥2 symptoms present | n, % | 342 | 81% | 196 | 81% | 99 | 83% | 12 | 75% | 0.76 |
| Menorrhagia severity | median, IQR | 3 | 2–4 | 3 | 2–4 | 3 | 2–4 | 3 | 2–4 | 0.10 |
| 0: no menorrhagia | n, % | 64 | 15% | 41 | 17% | 13 | 11% | 1 | 6% | |
| 1: consultation only | n, % | 29 | 7% | 19 | 8% | 5 | 4% | 1 | 6% | |
| 2: antifibrinolytics or pill use | n, % | 98 | 23% | 46 | 19% | 31 | 26% | 5 | 31% | |
| 3: dilatation and currettage or iron therapy | n, % | 121 | 29% | 74 | 31% | 37 | 31% | 3 | 19% | |
| 4: blood transfusion, FVIII/VWF concentrate, desmopressin or hysterectomy | n, % | 111 | 26% | 62 | 26% | 34 | 28% | 9 | 56% | |

* Chi square or ANOVA test for differences between subgroups. IQR, interquartile range.

**Excessive menstrual bleeding 83% 82% 81%**

# Prevalence of VWD in adolescents with menorrhagia

**Tab. 1** Prevalence studies in bleeding disorders associated with menorrhagia in adolescents

| study (ref.) | n | setting | VWD (%) |
|---|---|---|---|
| Chi et al. 2010 (22) | 42 | haemophilia treatment centre | 20 |
| Mikhail et al. 2007 (19) | 61 | outpatient haematology clinic | 36 |
| Jaysainghe et al. 2005 (17) | 106 | inpatient and outpatient | 5 |
| Philipp et al. 2004 (12) | 25 | outpatient primary care clinic | 4 |
| Kanbur et al. 2004 (18) | 47 | inpatient | 4 |
| Bevan et al. 2001(14) | 71 | emergency department, urgent care and inpatient | 3 |
| Oral et al. 2001 (20) | 25 | inpatient | 8 |
| Smith et al. 2001 (21) | 46 | | 5 |
| Falcone et al. 1994 (16) | 61 | | 0 |
| Claessens et al. 1981 (15) | 59 | | 8 |

Prevalence 3-36%

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

*Haemophilia* (2013), **19**, 71–75

DOI: 10.1111/hae.12012

ORIGINAL ARTICLE *Women with bleeding disorders*

# Menstrual bleeding patterns and prevalence of bleeding disorders in a multidisciplinary adolescent haematology clinic

K. T. VO,* L. GROOMS,† J. KLIMA,‡ C. HOLLAND-HALL*§ and S. H. O'BRIEN*†‡

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Haemophilia
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*Haemophilia* (2013), **19**, 71–75

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ORIGINAL ARTICLE *Women with bleeding disorders*

# Menstrual bleeding patterns and prevalence of bleeding disorders in a multidisciplinary adolescent haematology clinic

**62 % were diagnosed with a bleeding disorder**

K. T. VO,* L. GROOMS,† J. KLIMA,‡ C. HOLLAND-HALL*§ and S. H. O'BRIEN*†‡

**Department of Pediatrics, The Ohio State University/Nationwide Children's Hospital, Columbus, OH, USA; †Division of Pediatric Hematology/Oncology/BMT, Nationwide Children's Hospital, Columbus, OH, USA; ‡Center for Innovation in Pediatric Practice, The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA; and §Division of Adolescent Medicine, Nationwide Children's Hospital, Columbus, OH, USA*

# Review „Haemostatic variables during normal cycle“



## Haemostatic variables during normal menstrual cycle

### A systematic review

H. Marieke Knol[1,2]; Ramses F. J. Kemperman[3]; Hanneke C. Kluin-Nelemans[1]; André B. Mulder[3]; Karina Meijer[1]

[1]Division of Haemostasis and Thrombosis, Department of Haematology, University Medical Centre Groningen, Groningen, The Netherlands; [2]Department of Obstetrics and Gynaecology, University Medical Centre Groningen, Groningen, The Netherlands; [3]Department of Laboratory Medicine, University Medical Centre Groningen, Groningen, The Netherlands

**Summary**

For a number of haemostatic factors menstrual cycle variation has been studied. Such variation could have clinical implications for the timing of haemostatic testing in women. It was our objective to systematically review the literature about evidence for timing of haemostatic testing during menstrual cycle.We searched MEDLINE, EMBASE and the Cochrane library to identify studies that measured haemostatic variables [platelet function, von Willebrand factor (VWF), factor VIII (FVIII), factor IX (FIX), factor XI (FXI), factor XIII (FXIII), D-dimer, plasminogen activator inhibitor-I (PAI-I), tissue plasminogen activator (tPA), urokinase-type plasminogen activator (uPA), $\alpha_2$-antiplasmin and fibrinogen] during normal menstrual cycle without hormonal contraceptives. Two investigators independently selected studies, and abstracted data in duplicate. We identified 1,046 studies of which we included 30 studies (25 longitudinal and 5 cross-sectional studies). All studies reported on haemostatic variables during menstrual cycle. Overall, most of the studies found no cyclic variation in VWF, FVIII, FXI, FXIII, fibrinolytic factors (PAI, t-PA, uPA, D-dimer and $\alpha_2$-antiplasmin) and fibrinogen. However, in studies where these variables showed any variation, they reached the lowest levels during menstrual and early follicular phase, especially for VWF, FVIII and platelet function tests. In conclusion, the optimal timing for haemostatic testing during menstrual cycle seems to be menstrual and early follicular phase.

**Keywords**

Menstrual cycle, haemostasis, von Willebrand factor, haemostatic variables

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Prepublished online: December 8, 2011
**doi:10.1160/TH11-07-0481**
**Thromb Haemost 2012; 107: 22–29**

Knol H.M. et al. Thromb Haemost 2012; 107:22-29

# Review „Haemostatic variables during normal cycle“

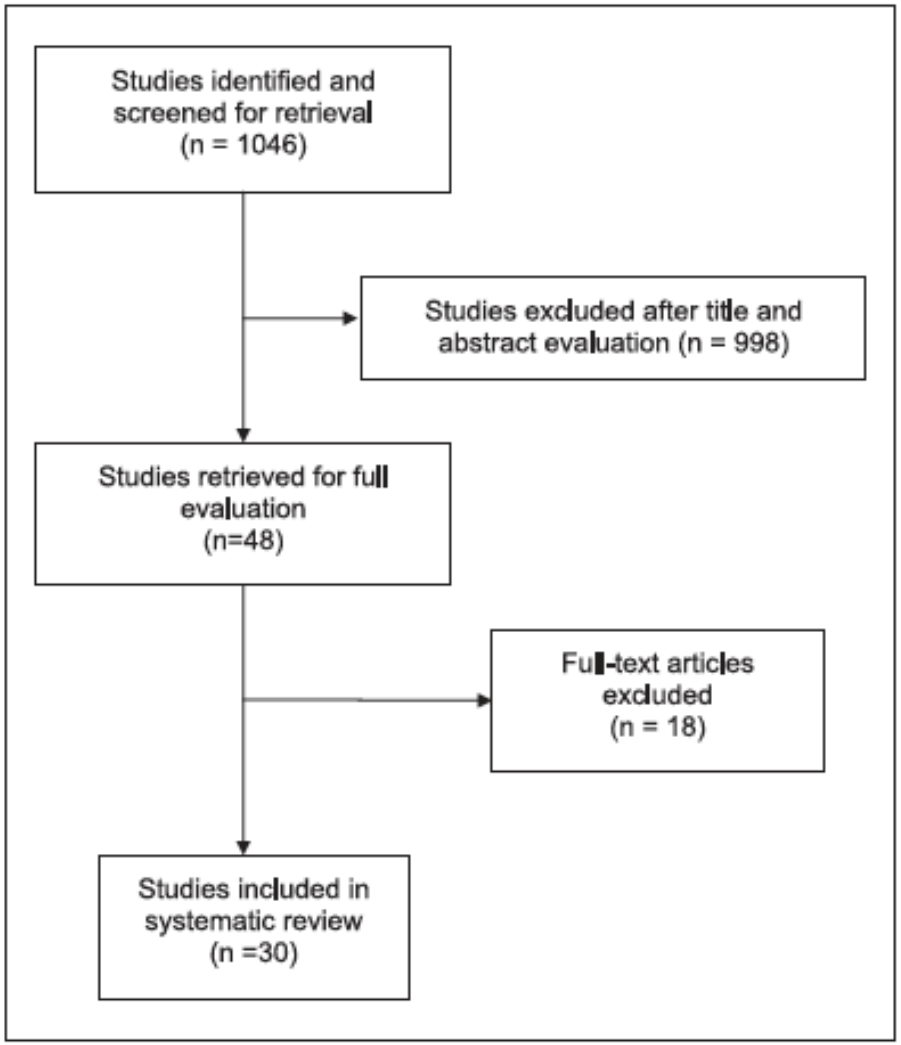



**Figure 1: Study flow diagram.**

Knol H.M. et al. Thromb Haemost 2012; 107:22-29

# Review „Haemostatic variables during normal cycle“ Results I

**Table 2: von Willebrand factor and factor VIII during the menstrual cycle.**

| Study | Number of patients | Haemostatic factors | Hormone analysis Y/N | Levels lowest in (cd or phase) | Measurement (cd or phase) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1 | 2 | 3 | 4 | 5 | 6 |
| Roell et al, 2007 (9) | 52 | vWF-ag | Y | mid F | mid F | mid L | | | | |
| Koh et al, 2005 (14) | 30 | FVIII, vWF | N | NA | 1–3 | 5–9 | 10–14 | 21–26 | | |
| Giardina et al, 2005 (12) | 20 | vWF-ag | Y | NA | F | L | | | | |
| Repina et al, 2002 (8) | 10 | FVIII | Y | NA | F | L | | | | |
| Feuring et al, 2002 (7) | 18 | vWF | Y | NA | 8–11 | 18–21 | | | | |
| Miller et al, 2002 (16) | 90 | FVIII; vWF-ag, vWF-RCF | N | 1–4 | 1–4 | 5–7 | 8–11 | 12–16 | 17–21 | 22–30 |
| Onundarson et al, 2001 (15) | 95 | vWF-ag, vWF-RCF, FVIII | Y | NA | 4–7 | 11–15 | 21–28 | | | |
| Kadir et al, 1999 (17) | 142 † | vWF-ag, vWF-RCF, FVIII | N | 1–3 (VWF-ag/RCF) | 1–4 | 6–11 | 10–18 | 20–25 | | |
| He et al, 1999 (18) | 24 | vWF-ag | N | NA | 5–7 | 24–26 | | | | |
| Blomback et al, 1997 (11) | 15 | vWF-ag, FVIII | Y | 5–7 (vWF-ag) | 5–7 | 20–25 | | | | |
| Blomback et al, 1992 (10) | 10 | vWF-ag, FVIII | Y | NA | unknown | | | | | |
| Jern et al, 1991 (13) | 9 | vWF-ag | Y | NA | 2–8 | 18–26 | | | | |
| Siegbahn et al 1989 (20) | 13 | FVIII | Y | NA | early F | late F | early L | late L | M | |
| Mandalaki et al, 1980 (19) | 9 | FVIII:C; FVIII:ag; VIII:RCF | N | 5–7 | 5–7 | 14 | 20 | 1 | | |

F= follicular phase; O= ovulation; L= lutheal phase; M= menstruation; cd=cycle days; NA= not applicable (no cyclic variation). † = 123 of them were menorragia patients. Y=yes; N=no; vWF= von Willebrand factor; ag= antigen; RCF= ristocetin cofactor.

Knol H.M. et al. Thromb Haemost 2012; 107:22-29

# Our own study

- 94 females, age 12 – 45 years (Median 24 years) were included
  - Menarche since 2 years was required*
- PBAC-Score 80 - 1735 (Median 227,5)
- The following tests were conducted:
  - VWF:RCo, VWF:Ag, VWF:CB,
  - Fibrinogen (Clauss),
  - Activity tests for FII, FV, FVII, FVIII (clotting und chromogen), FIX, FX, FXI, FXII and FXIII
  - During the cycle on the specified day:
    1-6, 7-11, 12-18, 19-23, 24-28

*because of anovulatory cycles

# Diagnosis of coagulation disorders (Total cohort n = 94)

- In 47/94 (50%) of the patients  a VWS was diagnosed
- 38/94 (40,4%) suffer from other coagulation disorders
- 9/94 (9,6%) have no coagulation disorders

| Coagulation disorder | n = patients |
|---|---|
| Factor XIII deficiency | 13 |
| Factor VII deficiency | 6 |
| Carrier of Haemophilia A | 2 |
| Factor V deficiency | 4 |
| Platelet function disorders | 19 |

Sums up to 44 as patients with more than one coagulation disorder were counted for each.

# Diagnosis of coagulation disorders (VWD; n = 47)

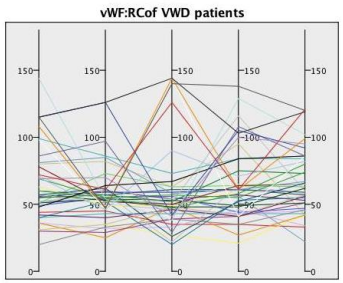
- In 47/94 (50%) of the patients  a VWS was diagnosed
- The following other coagulation disorders were diagnosed additionally to VWD

| Additional to von Willebrand disease | n = patients (total 47) |
|---|---|
| Factor VII deficiency | 3 |
| Factor XIII deficiency | 5 |
| Platelet function disorder | 4 |

patients with more than one coagulation disorder were counted for each.

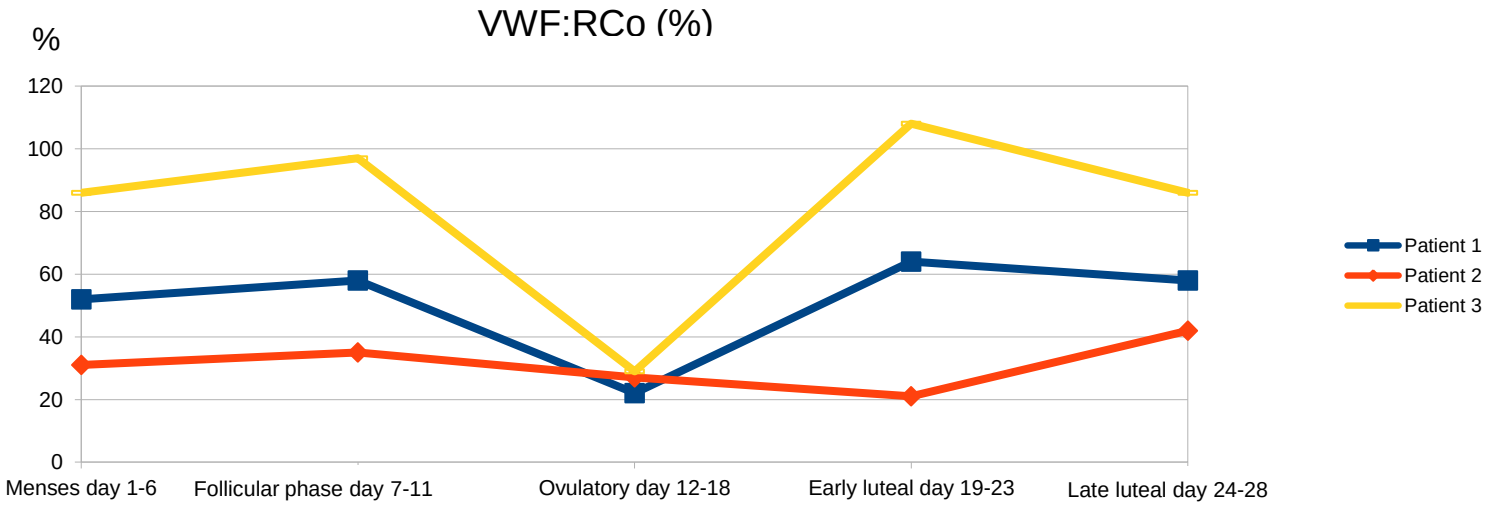
# Hypothesis testing process - VWF:RCo (n = 47)

- Null hypothesis:
  **No difference** between VWF:RCo on the specified day of cycle (1-6, 7-11, 12-18, 19-23, 24-28)
- Test method:
  Friedman two-way analysis of variance to compare
  > 3 paired groups
- P < .05 correlation coefficient is significantly different from zero
- Correlation coefficient VWF:RCo
  p = .0252 → data fail to reject the null hypothesis



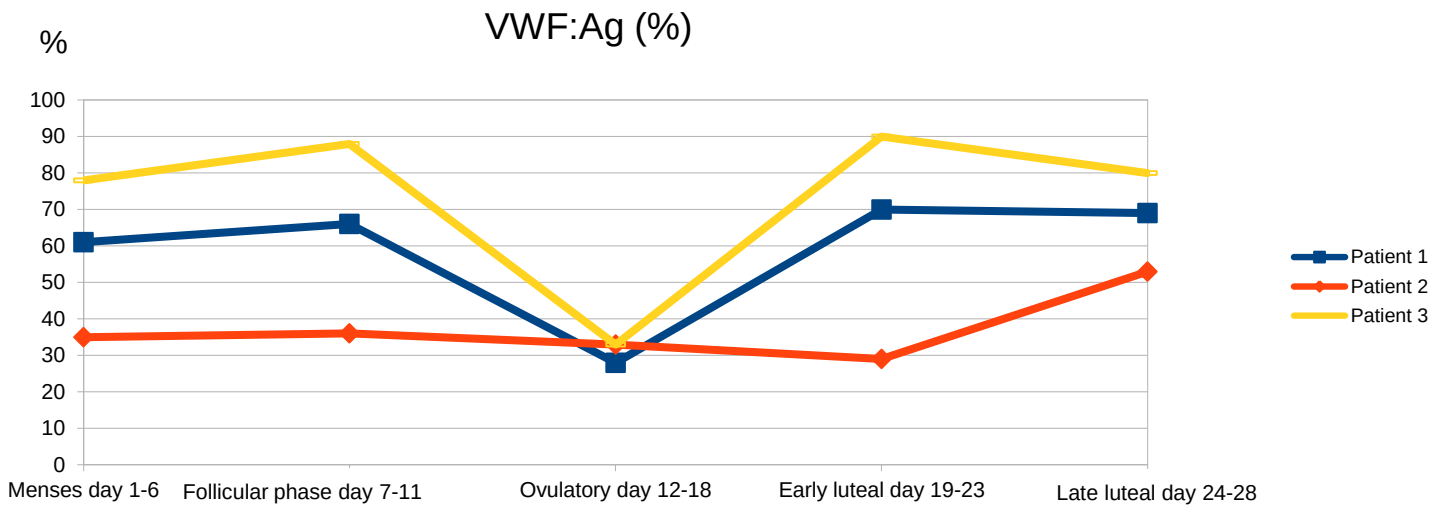
# VWF:RCo in patients with VWD (n = 3)

| | Menses Day1-6 | Follicular Phase Day7-11 | Ovulation Day12-18 | Early luteal Phase Day19-23 | Late luteal Phase Day 24-28 |
|---|---|---|---|---|---|
| Patient 1 | 52 | 58 | 22 | 64 | 58 |
| Patient 2 | 31 | 35 | 27 | 21 | 42 |
| Patient 3 | 86 | 97 | 29 | 108 | 86 |



# VWF:Ag in patients with VWD (n = 3)

| | Menses Day 1-6 | Follicular Phase Day 7-11 | Ovulation Day 12-18 | Early luteal Phase Day 19-23 | Late luteal Phase Day 24-28 |
|---|---|---|---|---|---|
| Patient 1 | 61 | 66 | 28 | 70 | 69 |
| Patient 2 | 35 | 36 | 33 | 29 | 53 |
| Patient 3 | 78 | 88 | 33 | 90 | 80 |



# Diagnosis of coagulation disorders _< 19 (Total cohort n = 16)

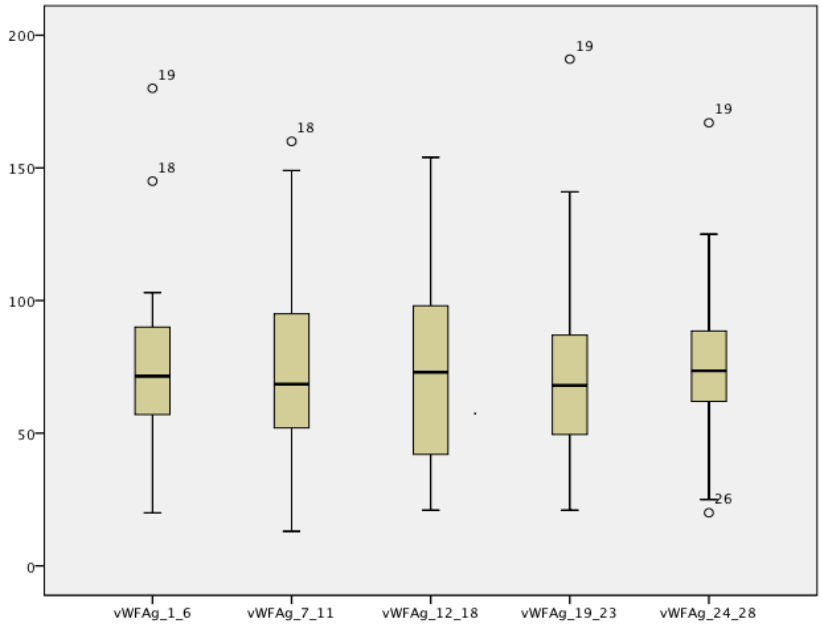
- In 7/16 (43.8%) of the patients  a VWS was diagnosed
- 4/16 (25%%) suffer from other coagulation disorders
- 5/16 (31.2%) have no coagulation disorders

| Coagulation disorder | n =  11 patients |
|---|---|
| Factor XIII deficiency | 3 |
| Factor VII deficiency | 1 |

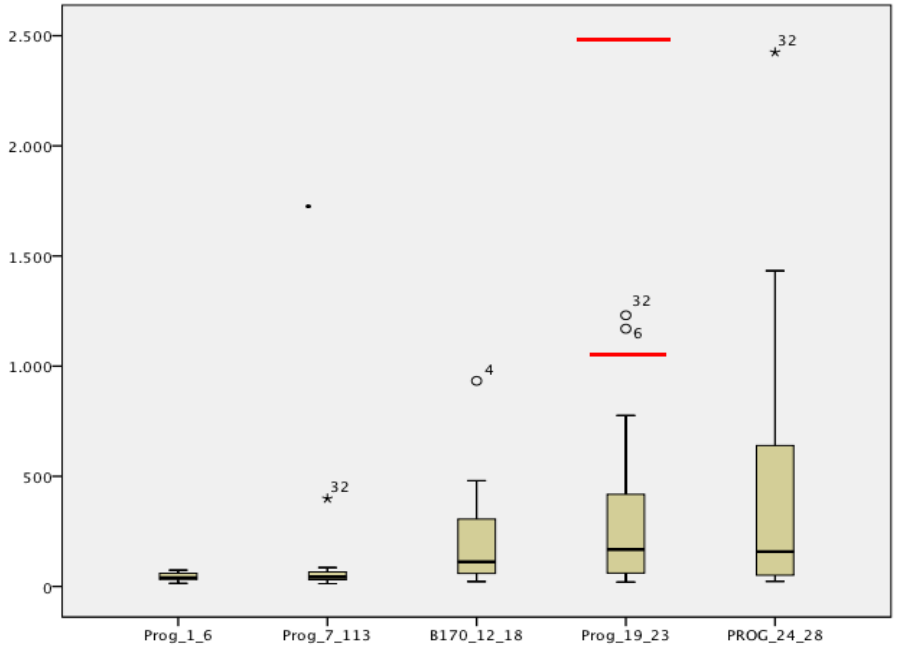
Sums up to 44 as patients with more than one coagulation disorder were counted for each.

# VWF:Ag in women with menorrhagia < 19 years (n = 16)

## VWF:Ag




## Progesteron

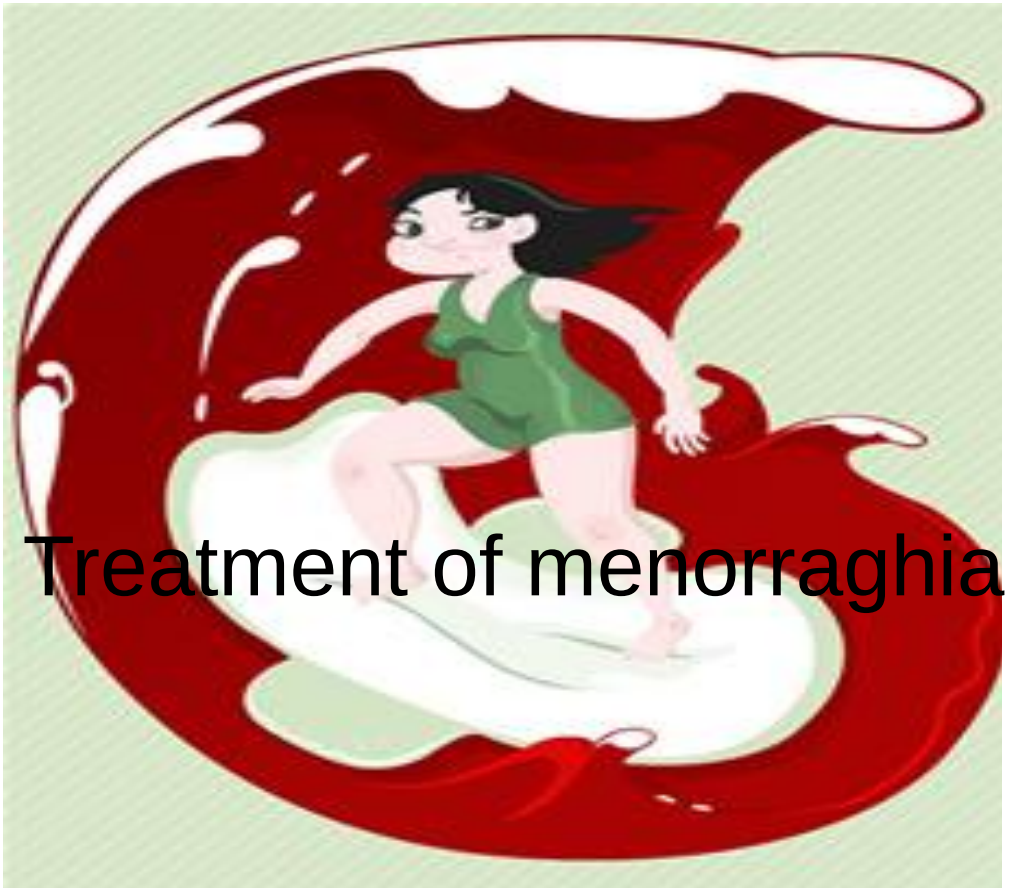


## B17O Ergebnisse Patientinnen

| | Referenzwert | Median | Mittelwert | Min | Max |
|---|---|---|---|---|---|
| Proliferative Phase | 45 - 140 | 34.25 | 38.37 | 12.3 | 107 |
| Ovulation | 200 - 500 | 91 | 191.54 | 22.3 | 933 |
| Lutealphase | 90 - 220 | 109 | 128.22 | 12.7 | 394 |

## Progesteron Ergebnisse Patientinnen

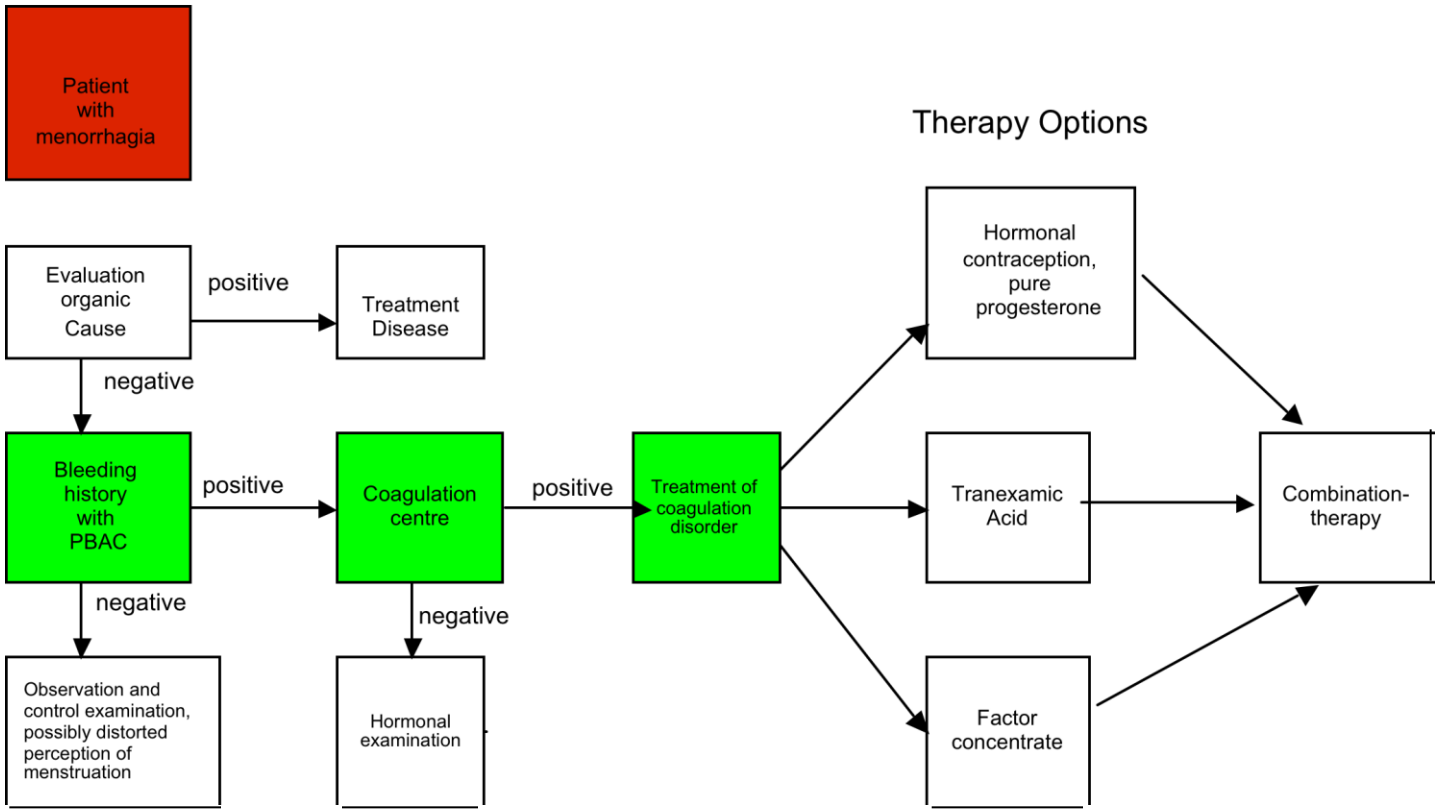
| | Referenzwert | Median | Mittelwert | Min | Max |
|---|---|---|---|---|---|
| Proliferative Phase | < 150 | 33.65 | 38.97 | 3 | 74.3 |
| Ovulation | | 61.2 | 111.17 | 3 | 578 |
| Lutealphase | 1100 - 2500 | 75.1 | 453.64 | 23.3 | 2425 |



# Treatment of menorraghia

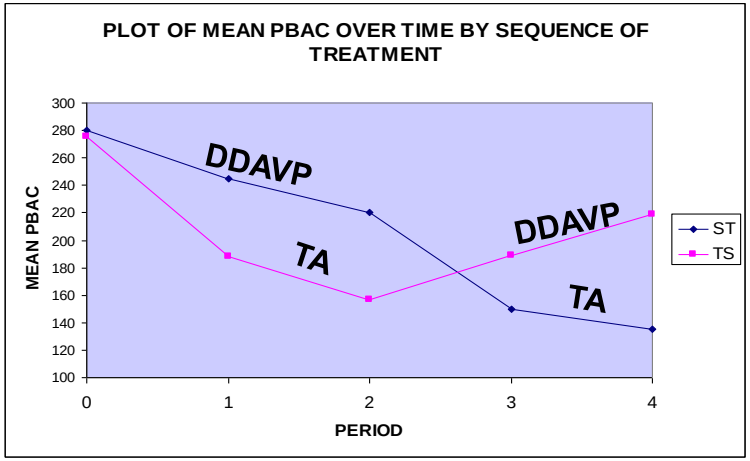
# Treatment of acute und chronic menorrhagia

**Figure 2**



# Treatment - Haemostatic

## Tranexamic acid and DDAVP (IN spray) - RCT in 116 women




**TA and DDAVP**

- **Improved HRQOL**
- **SF36**
- **CES-D**
- **RUTA**

Kouides 2009

**Combination of TA+DDAVP**

**Improve efficacy**
**Shorter duration and smaller dose DDAVP**
**Reduce adverse effects**

Edlund 2003

# Valette ® und Maxim ®




30µg Ethinylestradiol +
2mg Dienogest



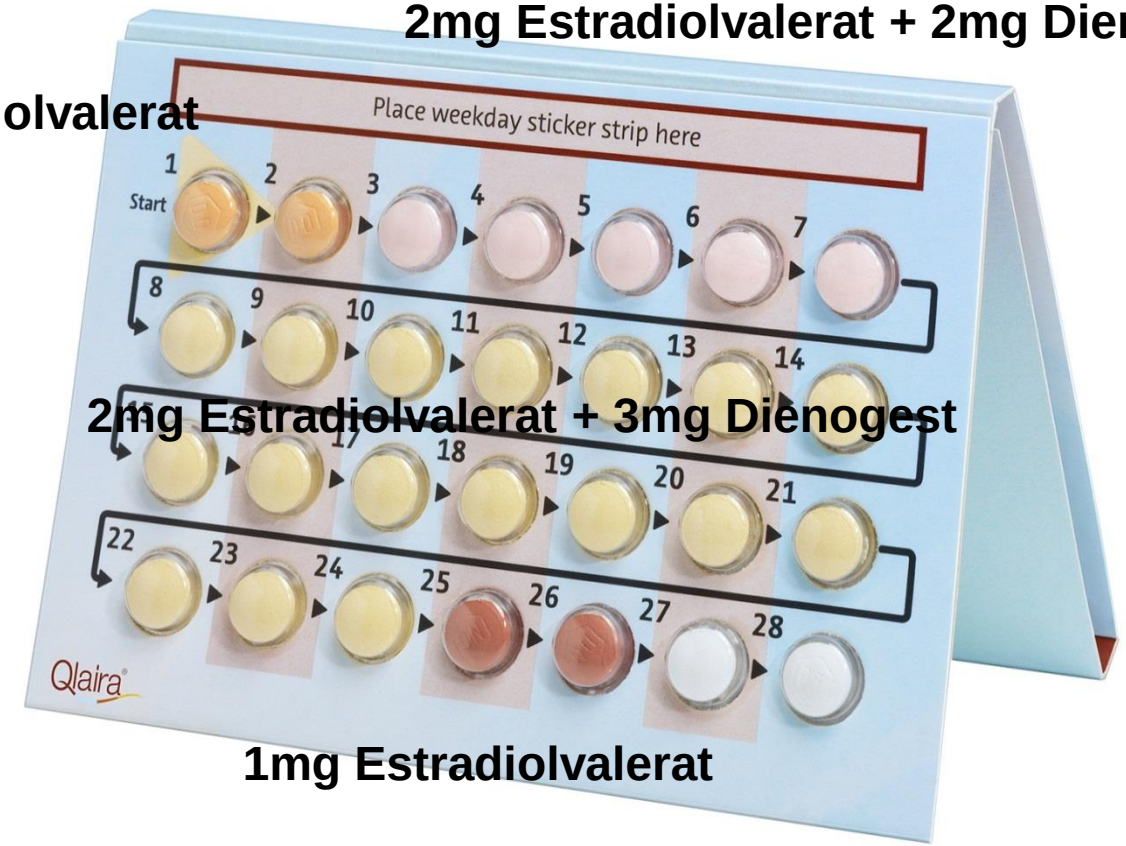

COC pill 4,3,2,1
until the bleed stops

Cave: thrombosis

# Qlaira® Wallet

2mg Estradiolvalerat + 2mg Dienogest

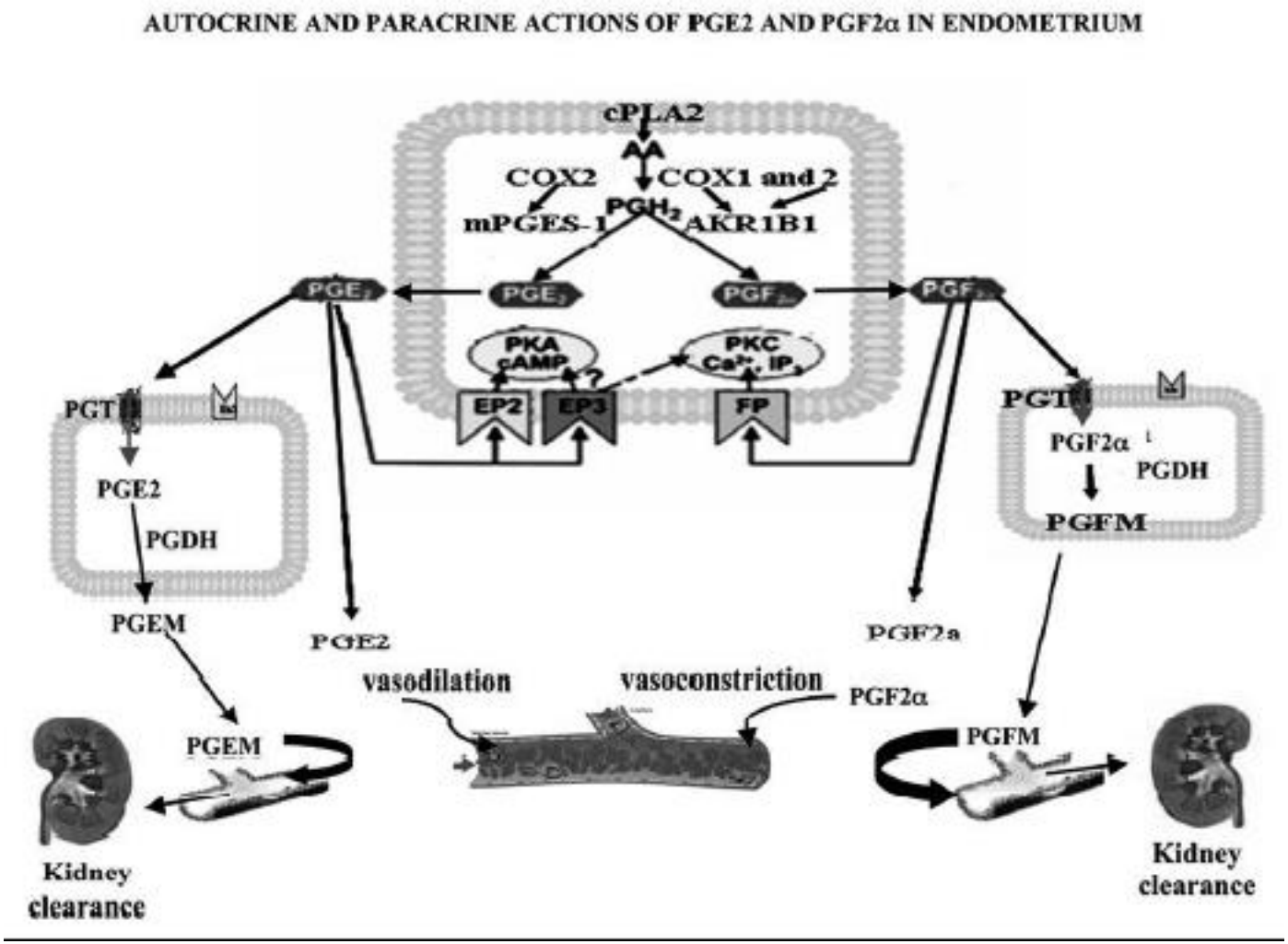
3mg Estradiolvalerat



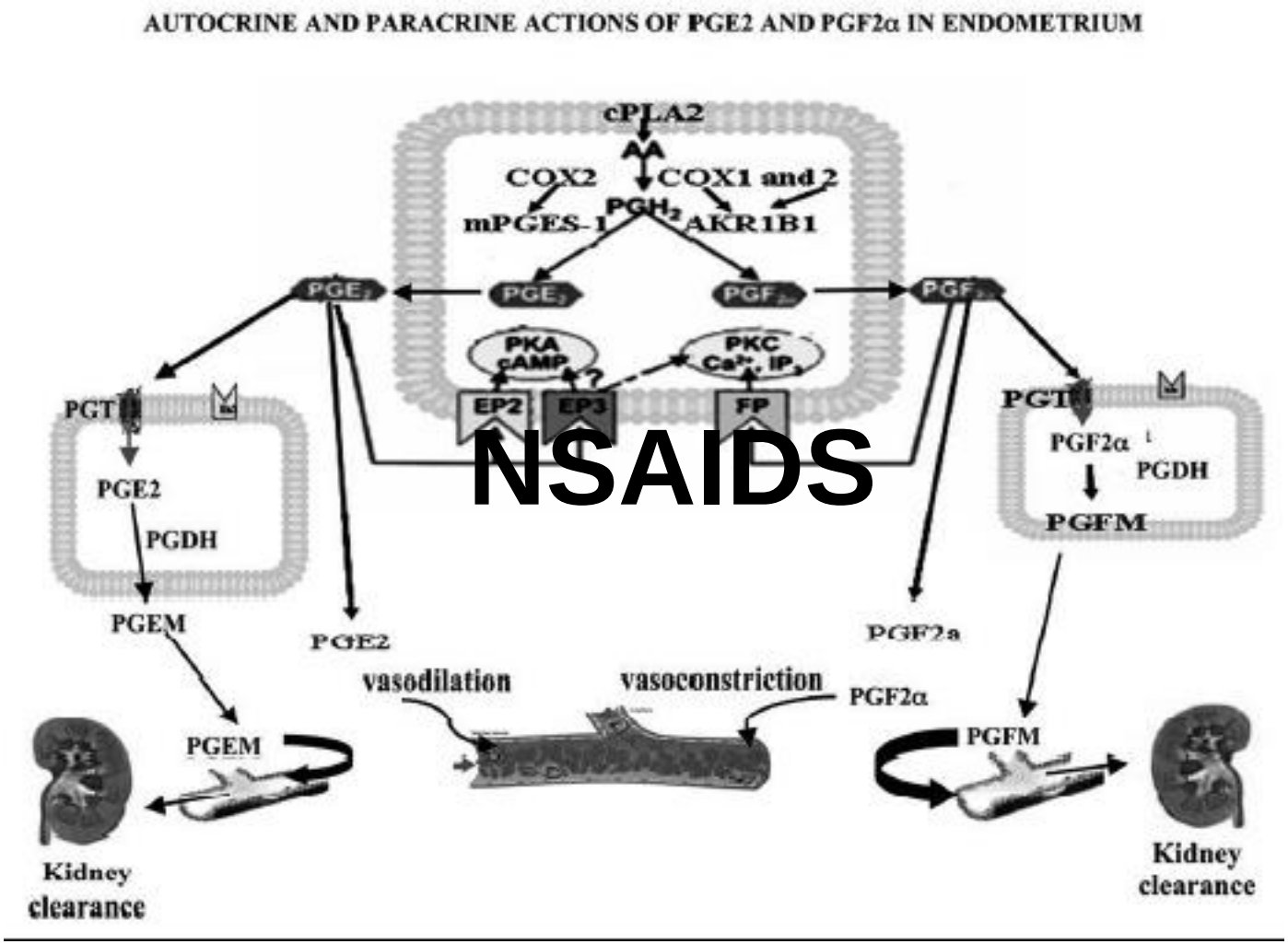

2mg Estradiolvalerat + 3mg Dienogest

1mg Estradiolvalerat

# Mechanism of PGF2 and PGE2



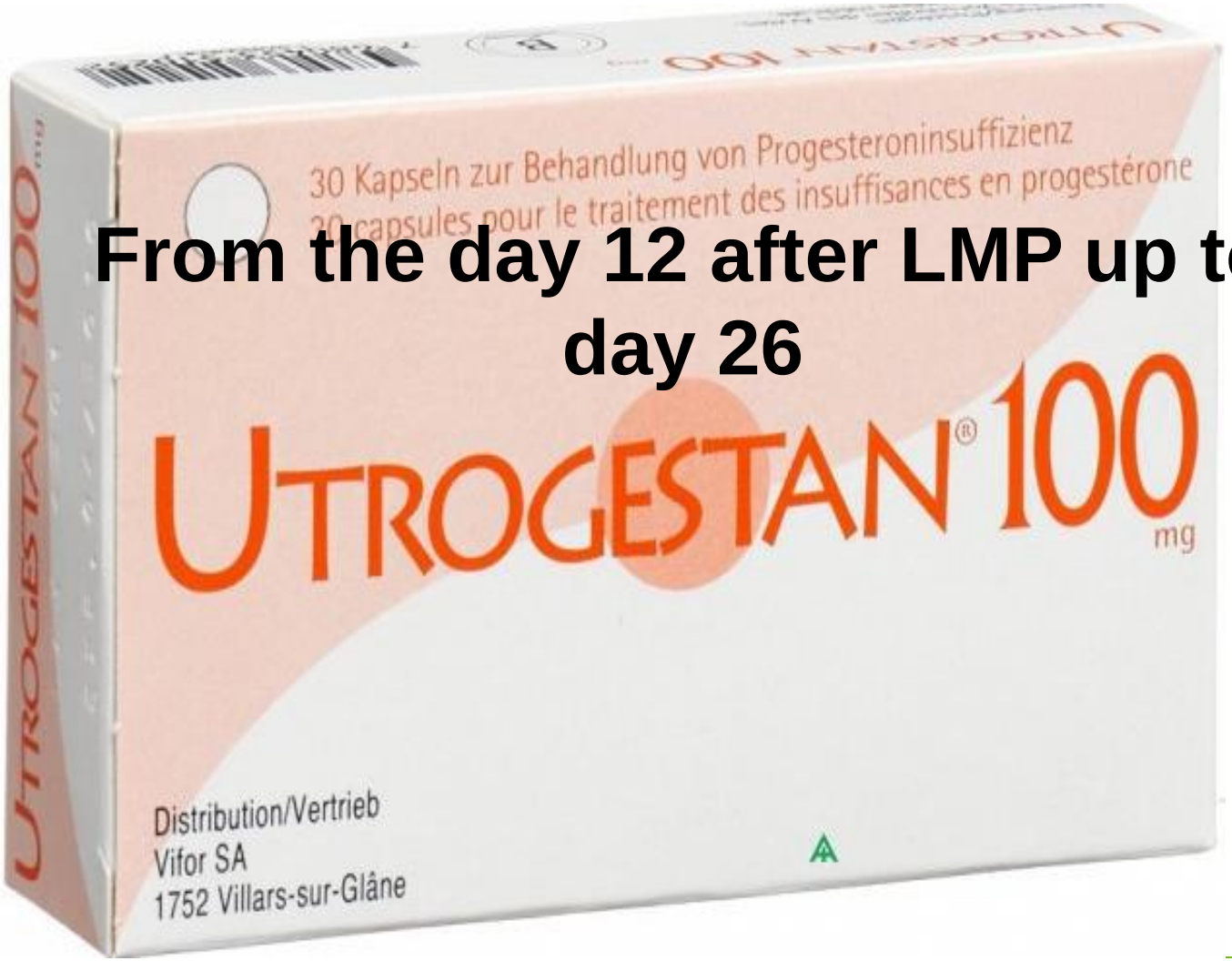
# Mechanism of PGF2 and PGE2



# Utrogestan 100

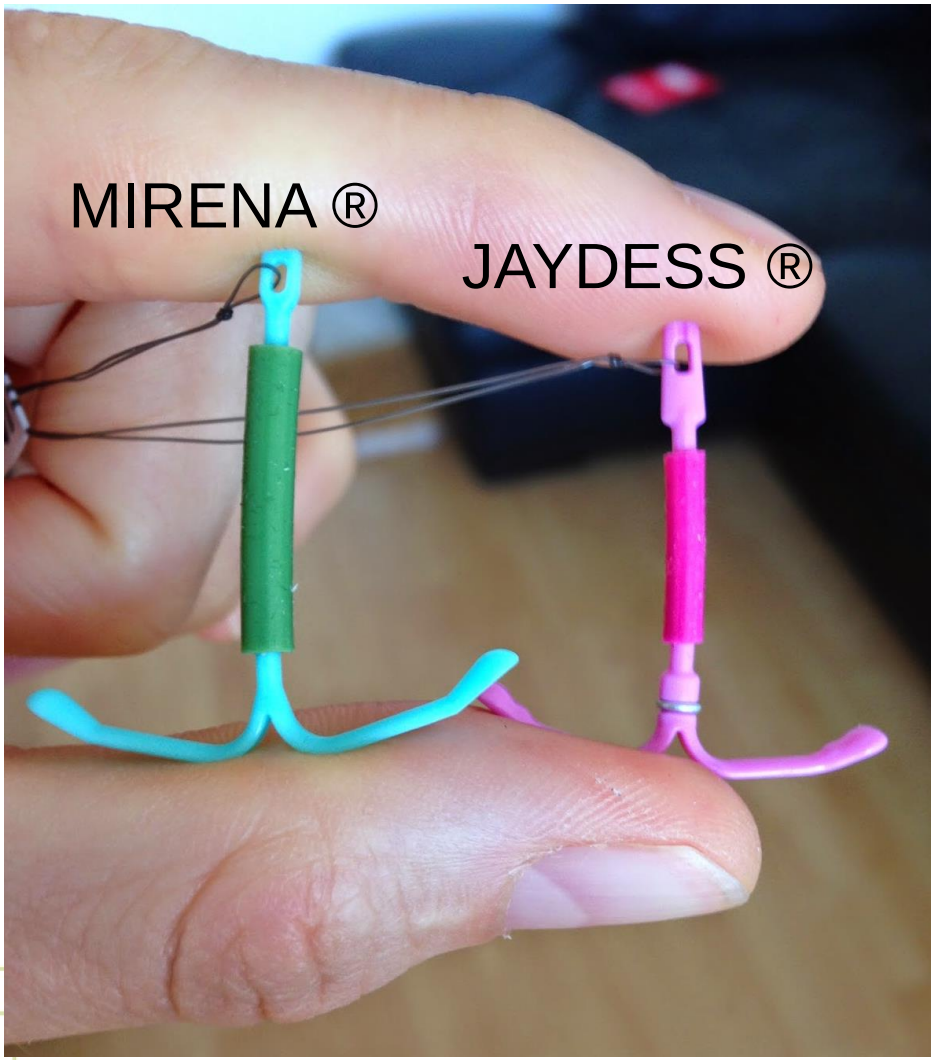


# Utrogestan 100




**From the day 12 after LMP up to day 26**

# LNG-IUS (Mirena- Jaydess)-Women with bleeding disorders




## Other Possible Health Benefits

- Most effective reversible contraceptive (5 yr) – (3yr)
- Menstrual pain &PMS
- Endometrial hyperplasia
- Endometriosis, adenomyosis /fibroid

Kingman 2004
Chi, 2010

# Take home message

- **To be aware about menorrhagia in adolescence**
- **It is good detected with the PBAC score**
- **Different ages and situations need different treatment**

dr. rott
dr. halimeh
dr. kappert

gerinnungs
zentrum
rhein-ruhr

# Management of PPH

Dr. med. Susan Halimeh

ORIGINAL ARTICLE

# Evaluation and management of postpartum hemorrhage: consensus from an international expert panel

*Rezan Abdul-Kadir,[1] Claire McLintock,[2] Anne-Sophie Ducloy,[3] Hazem El-Refaey,[4] Adrian England,[5] Augusto B. Federici,[6] Chad A. Grotegut,[7] Susan Halimeh,[8] Jay H. Herman,[9] Stefan Hofer,[10] Andra H. James,[11] Peter A. Kouides,[12] Michael J. Paidas,[13] Flora Peyvandi,[14] and Rochelle Winikoff[15]*

Transfusion Nov. 2013

# Definition of PPH

| Guidelines | Definition |
|---|---|
| Australian 2008 | Blood loss >500 ml after vaginal delivery and >750 ml following cesarean section |
| Austrian Guidelines 2008 | Blood loss of 500–1000 ml and clinical signs of hypovolemic shock or blood loss >1000 ml |
| German Guidelines 2008 | Blood loss ≥500 ml within 24 hours after birth. Severe PPH is blood loss ≥1000 ml within 24 hours. |
| RCOG 2009 | Primary PPH involving an estimated blood loss of 500–1000 ml (and in the absence of clinical signs of shock) should prompt basic measures (close monitoring, intravenous access, full blood count, group and screen) to facilitate resuscitation should it become necessary.<br>If a woman with primary PPH is continuing to bleed after an estimated blood loss of 1000 ml (or has clinical signs of shock or tachycardia associated with a smaller estimated loss), this should prompt a full protocol of measures to achieve resuscitation and hemostasis. |
| WHO definition | Blood loss ≥500 ml within 24 hours after birth. Severe PPH is blood loss ≥1000 ml within 24 hours. |

# Definition of PPH

| Guidelines | Definition |
|---|---|
| Australian 2008 | Blood loss >500 ml after vaginal delivery and >750 ml following cesarean section |
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| German Guidelines 2008 | Blood loss ≥500 ml within 24 hours after birth. Severe PPH is blood loss ≥1000 ml within 24 hours. |
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| WHO definition | Blood loss ≥500 ml within 24 hours after birth. Severe PPH is blood loss ≥1000 ml within 24 hours. |

RISK: > 1500 ml

Wise A et al. Curr Opin Anaestiol 2008
McLintock C. Thromb Res 2009

# Incidence of maternal mortality

- Causes for the maternal mortality in industrial countries

- **1.Thromboembolism; 2.hypertension, 3.PPH**
- Strong bleeding - 10-15% of all  Caesarean sections

- Acute threatening bleeding: 1:1000 deliveries

**INCREASING** in industrial contries (1,2% 2008 in England, 1,5% 2009 in France

Gil-Gonzalez D et al. Bull World Health Organ 2006
Sundaram R et al. Anaesthesia 2006
Bonnar J. Baillieres Best Pract Res Clin Obstet Gynaecol 2000
Samanfaya RA et al BJOG 2010
Dupont C et al. IJOA 2009

# Reasons for maternal mortality

**In Europe 13.4% PPH**

**Third place for maternal mortality**

Khan KS et al. WHO analysis of causes of maternal death:a systematic review. Lancet 2006; 367: 1066-1074

# PPH

**75- 90% of fetal bleeding are postpartal espesially within the first 4 hours postpartum**

Crombach G Gynäkologie 2000
Ramanathan G et al. J. Ostet Gynaecol Can 2006

# PPH

**Risk of PPH after a cesarian**
**4-times more than after a spontaneous delivery**

Crombach G Gynäkologie 2000

# PPH

**90% of mortality cases could be avoided**

Berg CJ et al. Obstet Gynecol 2005

# Risk factors associated with PPH

## 1. Sociol-demographic factors

- **Age >30 years**
- **Multipara ( ≥ 5)-** but also PPH by Primipara (OR 5,6)

  Malkiel et al. Isr. Med Assoc J 2008
- **Spanish or asiatic origin**
- **Nicotinabuse**
- **Gestational hypertension**
- **Risk of premature placenta Separation**

# Risk factors associated with PPH

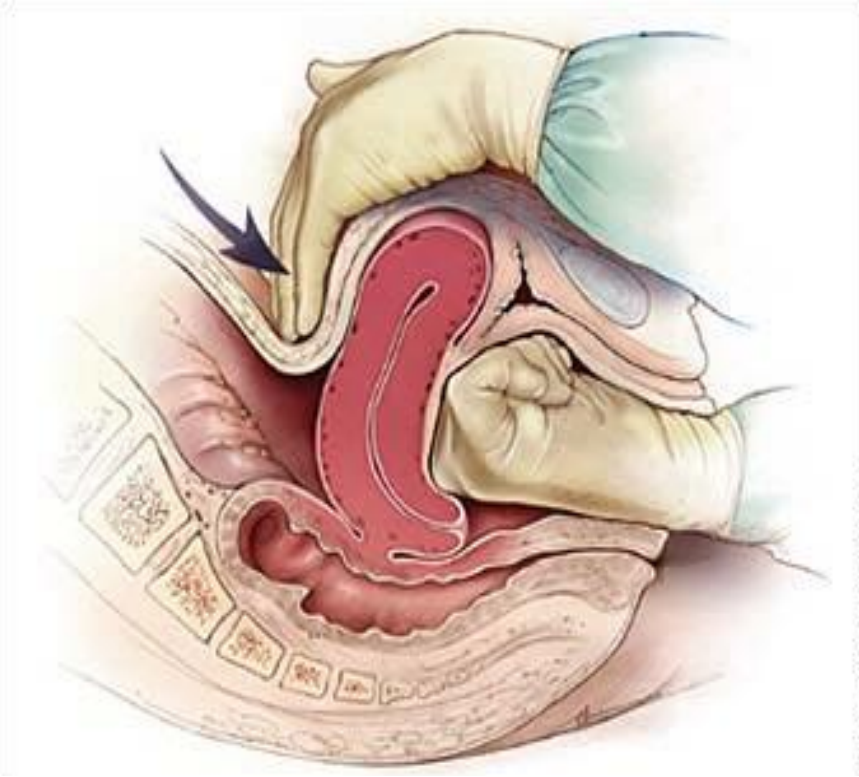
## 2. Gynecological factors

- **Uterine Atony**

80% of all patients with uterine atony show prepartal known riskfactors, only in 20% the bleeding occurs unexpectedely

The uterine atony bleeding are increasing in industrial countries

Knight M et al. BMC 2009



Crombach G Gynäkologie 2000

# Risk factors associated with PPH

## 2. Gynäkologische Faktoren

- In case Uterine Atony ➔ repeating risk up to 25%
- In cases of previous  cesarian section or curettage...
- Myoma
- Uterine enlargement (twins, polyhydramnion, transverse presentation,...)

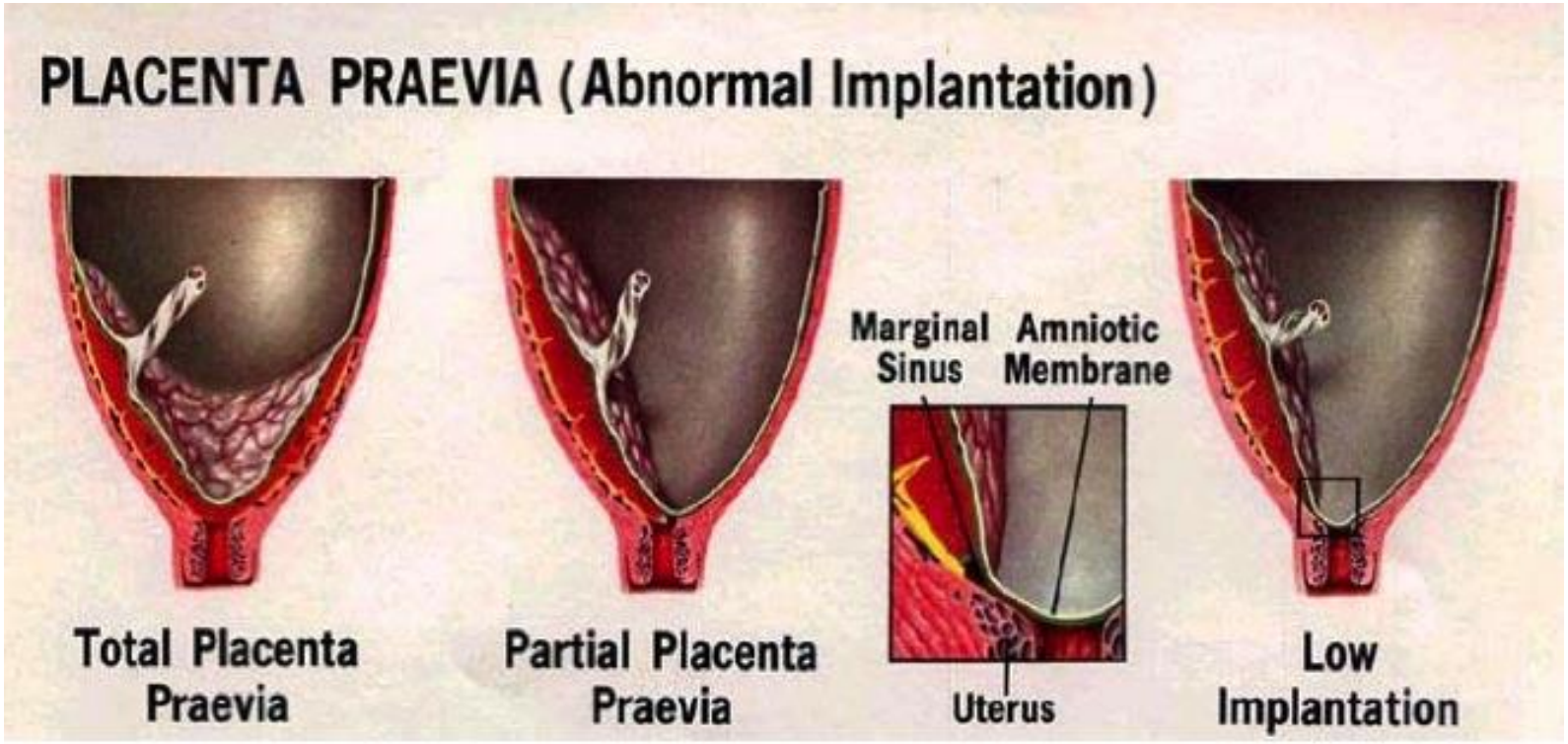
# Uterine Atony

- 70-80% of PPH

Bibi et al, J Ayub Medical College, Abbottobad, 19:102-6, 2007

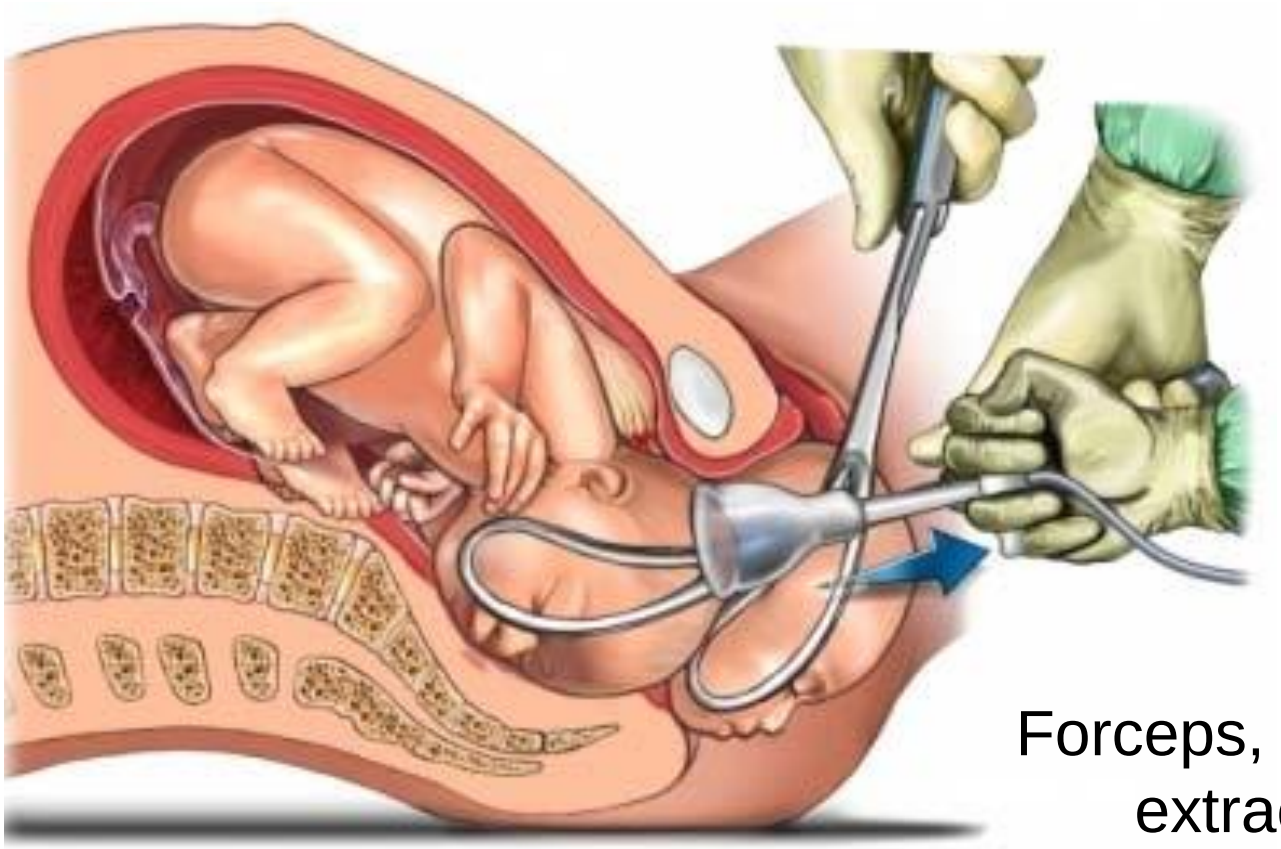
# Risk factors associated with PPH

3. Abnormal Placenta



# Risk factors associated with PPH

4. Instrumental interventions



Forceps, Vakuum extraction

# Risk factors associated with PPH

## 5. Haemostaseological factors

- ✓ Von Willebrand disease
- ✓ Carriers of haemophilia A
- ✓ Rare factors deficiency
- ✓ Platelet dysfunction

The 4t´s: ***tone*** (postpartale uterine Atony, ***tissue*** (Placental residuals), ***trauma*** **(injury of the birth canal**), ***thrombin*** (coagulapathy)

# Haemostais changes during pregnancy

- **Fibrinogen**
- **FVIII**
- **VWF**

~ 1.5-3 times
Cave postpartum

- **FVIIa → ~ 2 fach**
- **Thrombomodulin**
- **PAI-1**

- Platelets count
- Fibrinolytic Activity
- Free protein S

No significant variation of FII, FV and FIX

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CLINICAL ARTICLE

# Prospective, sequential, longitudinal study of coagulation changes during pregnancy in Chinese women

Xing-hui Liu [a], Yong-mei Jiang [b], Hua Shi [b], Xin-ai Yue [b], Yue-fang Wang [b], Hui Yang [b,*]

[a] Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, China
[b] Department of Laboratory Medicine, West China Second University Hospital, Sichuan University, Chengdu, China

232 women conducted from September 2006-December 2007

**Table 3**
Reference values for the most used hemostatic variables according to pregnancy trimester and after delivery[a].

| Variable | Study group [b] (n=120) | | | | Controls (n=120) |
|---|---|---|---|---|---|
| | 1st trimester | 2nd trimester | 3rd trimester | Postpartum | |
| Prothrombin time, sec | 11.80 (10.50–12.90) | 11.60 [c,d] (10.50–12.60) | 11.70 (10.70–12.80) | 11.70 (10.30–12.70) | 11.90 (10.40–13.90) |
| INR | 0.95 (0.86–1.08) | 0.91 [c,d] (0.83–1.02) | 0.93 (0.84–1.09) | 0.93 (0.81–1.05) | 0.96 (0.82–1.90) |
| aPTT, sec | 28.70 [c] (23.00–37.10) | 26.90 [c,d] (22.90–33.40) | 26.70 [c,d] (22.60–32.80) | 29.7 (22.60–38.90) | 29.8 (24.40–36.40) |
| aPTT ratio | 0.98 [c] (0.79–1.16) | 0.94 [c,d] (0.82–1.14) | 0.91 [c,d,e] (0.77–1.10) | 1.01 (0.84–1.23) | 1.02 (0.87–1.20) |
| PC $\times 10^9$/L | 158 (~87 to 238) | 146 [c] (67–224) | 141 [c] (65–218) | 165 (74–255) | 171 (94–247) |
| MPV, fL | 12.1 (10.10–15.60) | 12.00 (10.00–14.00) | 12.20 (10.00–14.10) | 13.10 (11.10–14.80) | 12.6 (10.40–14.80) |
| Fibrinogen, g/L | 3.72 [c] (2.73–4.93) | 3.78 [c,d] (2.94–5.00) | 4.27 [c,d,e] (3.01–5.98) | 2.45 (1.76–3.60) | 2.38 (1.99–3.79) |
| FDP, µg/L | 30.00 (20.50–47.80) | 32.70 [c,d] (21.90–62.10) | 44.70 [c,d,e] (25.60–72.20) | 27.80 (16.50–47.80) | 28.70 (16.50–40.00) |

# Haemostatic reference intervals in pregnancy

Pal B. Szecsi[1]; Maja Jørgensen[2]; Anna Klajnbard[3]; Malene R. Andersen[1]; Nina P. Colov[3]; Steen Stender[1]

[1]Department of Clinical Biochemistry, Gentofte Hospital, University of Copenhagen, Denmark; [2]The Thrombosis Center, Gentofte Hospital, University of Copenhagen, Denmark; [3]Department of Obstetrics and Gynecology, Gentofte Hospital, University of Copenhagen, Denmark

## Summary

Haemostatic reference intervals are generally based on samples from non-pregnant women. Thus, they may not be relevant to pregnant women, a problem that may hinder accurate diagnosis and treatment of haemostatic disorders during pregnancy. In this study, we establish gestational age-specific reference intervals for coagulation tests during normal pregnancy. Eight hundred one women with expected normal pregnancies were included in the study. Of these women, 391 had no complications during pregnancy, vaginal delivery, or postpartum period. Plasma samples were obtained at gestational weeks 13–20, 21–28, 29–34, 35–42, at active labor, and on postpartum days 1 and 2. Reference intervals for each gestational period using only the uncomplicated pregnancies were calculated in all 391 women for activated partial thromboplastin time (aPTT), fibrinogen, fibrin D-dimer, antithrombin, free protein S, and protein C and in a subgroup of 186 women in addition for prothrombin time (PT), Owren and Quick PT, protein S activity, and total protein S and coagulation factors II, V, VII, VIII, IX, X, XI, and XII. The level of coagulation factors II, V, X, XI, XII and antithrombin, protein C, aPTT, PT remained largely unchanged during pregnancy, delivery, and postpartum and were within non-pregnant reference intervals. However, levels of fibrinogen, D-dimer, and coagulation factors VII, VIII, and IX increased markedly. Protein S activity decreased substantially, while free protein S decreased slightly and total protein S was stable. Gestational age-specific reference values are essential for the accurate interpretation of a subset of haemostatic tests during pregnancy, delivery, and puerperium.

## Keywords

Fibrin D-dimer, haemostasis, normal pregnancy, protein C, protein S, reference interval

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**Thromb Haemost 2010; 103: 718–727**

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## Summary

Haemostatic reference intervals are generally based on samples from non-pregnant women. Thus, they may not be relevant to pregnant women, a problem that may hinder accurate diagnosis and treatment of haemostatic disorders during pregnancy. In this study, we establish gestational age-specific reference intervals for coagulation tests during normal pregnancy. Eight hundred one women with expected normal pregnancies were included in the study. Of these women, 391 had no complications during pregnancy, vaginal delivery, or postpartum period. Plasma samples were obtained at gestational weeks 13–20, 21–28, 29–34, 35–42, at active labor, and on postpartum days 1 and 2. Reference intervals for each gestational period using only the uncomplicated pregnancies were calculated in all 391 women for activated partial thromboplastin time (aPTT), fibrinogen, fibrin D-dimer, antithrombin, free protein S, and protein C and in a subgroup of 186 women in addition for prothrombin time (PT), Owren and Quick PT, protein S activity, and total protein S and coagulation factors II, V, VII, VIII, IX, X, XI, and XII. The level of coagulation factors II, V, X, XI, XII and antithrombin, protein C, aPTT, PT remained largely unchanged during pregnancy, delivery, and postpartum and were within non-pregnant reference intervals. However, levels of fibrinogen, D-dimer, and coagulation factors VII, VIII, and IX increased markedly. Protein S activity decreased substantially, while free protein S decreased slightly and total protein S was stable. Gestational age-specific reference values are essential for the accurate interpretation of a subset of haemostatic tests during pregnancy, delivery, and puerperium.

## Keywords

Fibrin D-dimer, haemostasis, normal pregnancy, protein C, protein S, reference interval

- 801 patients
- 391 patients have no complications
- 186 patients all factors

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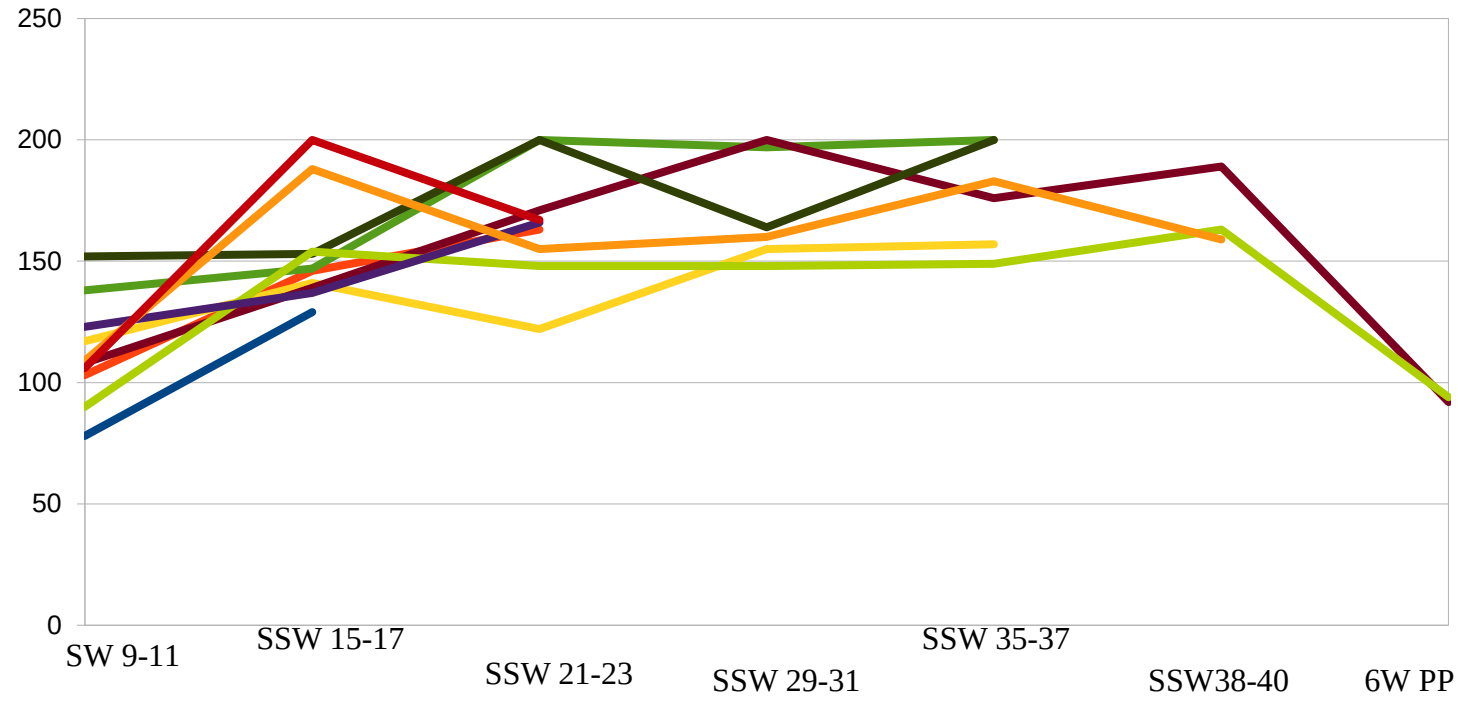
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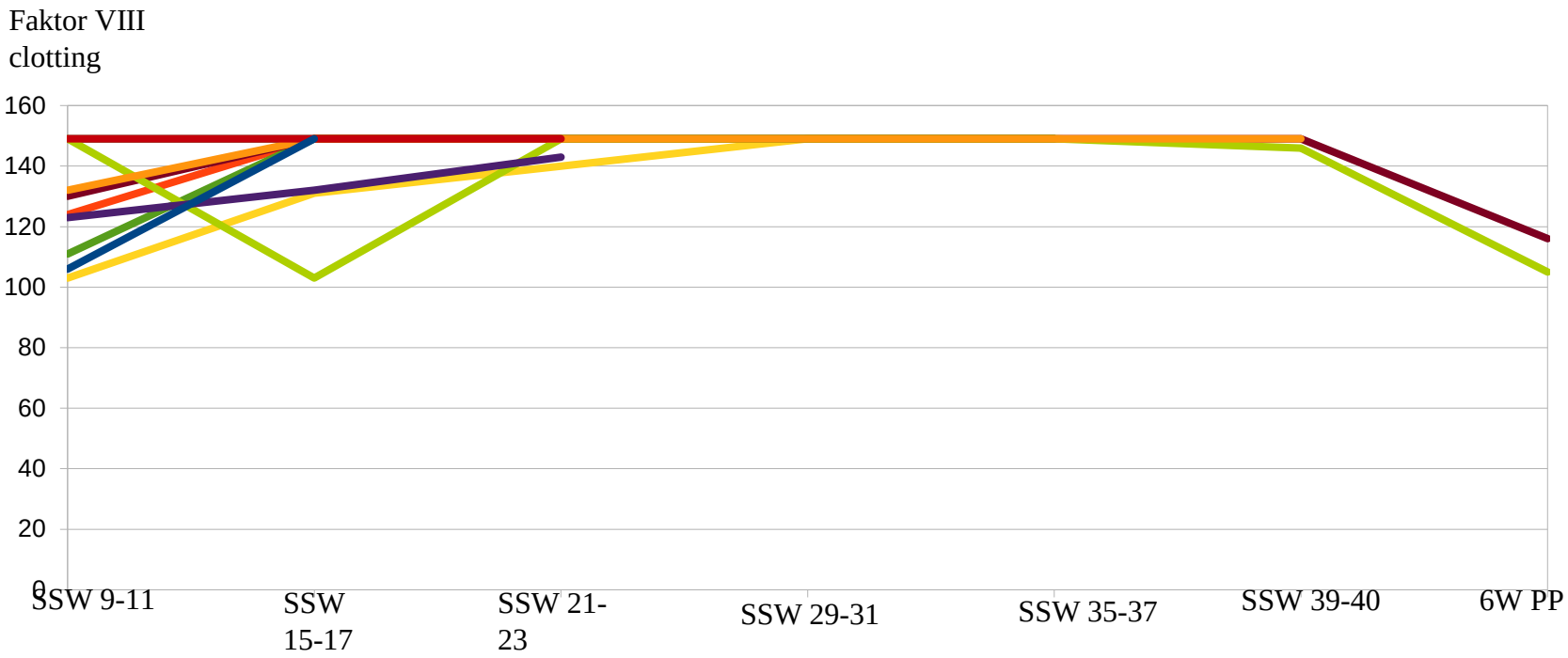
| Test | 13–20 weeks | | 21–28 weeks | | 29–34 weeks | | 35–42 weeks | | Partus | | Partus +1 | | Partus +2 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Protein S act | n=122 [0] | | n=58 [0] | | n=31 [0] * | | n=72 [0] * | | n=54 [0] * | | n=67 [0] * | | n=38 [1] * | |
| | 0.34 (0.33–0.40) | 0.93 (0.80–0.98) | 0.35 (0.35–0.36) | 0.81 (0.69–0.81) | 0.25 # | 0.85 # | 0.25 (0.22–0.27) | 0.86 (0.62–0.99) | 0.14 (0.11–0.22) | 0.59 (0.57–0.61) | 0.22 (0.19–0.26) | 0.54 (0.48–0.62) | 0.30 # | 0.81 # |
| Protein S free | n=535 [0] | | n=368 [0] * | | n=177 [0] * | | n=361 [0] * | | n=241 [0] * | | n=255 [0] * | | n=157 [0] | |
| | 0.37 (0.36–0.38) | 0.79 (0.78–0.84) | 0.37 (0.35–0.38) | 0.71 (0.69–0.73) | 0.31 (0.29–0.34) | 0.64 (0.60–0.68) | 0.31 (0.29–0.33) | 0.67 (0.64–0.72) | 0.32 (0.31–0.34) | 0.72 (0.66–0.77) | 0.31 (0.29–0.32) | 0.73 (0.68–0.80) | 0.37 (0.33–0.38) | 0.86 (0.79–1.02) |
| Protein S total | n=122 [0] | | n=58 [0] | | n=32 [0] | | n=71 [0] | | n=55 [0] | | n=67 [0] * | | n=37 [0] | |
| | 0.55 (0.53–0.57) | 1.00 (0.98–1.04) | 0.47 (0.45–0.53) | 1.02 (0.99–1.02) | 0.33 # | 0.98 # | 0.43 (0.33–0.47) | 1.06 (0.97–1.20) | 0.44 (0.43.0.50) | 1.04 (0.94–1.07) | 0.43 (0.39–0.47) | 1.00 (0.94–1.07) | 0.55 # | 0.98 # |
| Factor II | n=129 [0] | | n=56 [0] | | n=30 [0] | | n=73 [0] | | n=55 [0] | | n=65 [0] * | | n=37 [0] | |
| | 0.80 (0.76–0.83) | 1.18 (1.13–1.27) | 0.82 (0.80–0.88) | 1.28 (1.21–1.31) | 0.88 # | 1.21 # | 0.79 (0.76–0.83) | 1.29 (1.18–1.34) | 0.70 (0.68–0.83) | 1.15 (1.11–1.15) | 0.65 (0.63–0.75) | 1.25 (1.12–1.38) | 0.70 # | 1.24 # |
| Factor V | n=129 [0] | | n=56 [0] | | n=30 [0] | | n=73 [0] | | n=55 [0] | | n=65 [0] | | n=33 [1] * | |
| | 0.57 (0.49–0.63) | 1.22 (1.15–1.43) | 0.57 (0.52–0.66) | 1.28 (1.24–1.31) | 0.48 # | 1.29 # | 0.53 (0.40–0.64) | 1.27 (1.23–1.31) | 0.09 (0.02–0.53) | 1.35 (1.18–1.38) | 0.53 (0.49–0.67) | 1.35 (1.21–1.46) | 0.57 # | 1.58 # |
| Factor VII | n=128 [2] | | n=58[0] * | | n=31[0] * | | n=71[1] * | | n=31[1] * | | n=59 [1] * | | n=36 [0] * | |
| | 0.55 (0.42–0.72) | 1.84 (1.71–1.93) | 0.43 (0.10–0.84) | 2.24 (1.97–2.33) | 0.99 # | 2.11 # | 0.87 (0.77–1.06) | 2.51 (2.39–2.53) | 0.96 # | 3.30 # | 0.92 (0.86–1.09) | 2.46 (2.09–2.64) | 0.91 # | 2.29 # |
| Factor VIII | n=129 [0] | | n=56 [0] * | | n=30 [0] * | | n=73 [0] * | | n=25 [0] * | | n=56 [0] * | | n=33 [1] * | |
| | 0.82 (0.53–0.94) | 2.91 (2.38–3.35) | 0.96 (0.92–1.06) | 3.72 (3.34–3.92) | 0.89 # | 3.49 # | 1.30 (1.26–1.40) | 4.30 (3.60–4.36) | 1.31 # | 4.67 # | 1.25 (1.20–1.41) | 5.21 (3.97–6.00) | 1.15 # | 6.00 # |
| Factor IX | n=127 [0] | | n=55 [0] * | | n=28 [0] * | | n=72 [0] * | | n=55 [0] * | | n=64 [0] * | | n=39 [0] * | |
| | 0.84 (0.71–0.89) | 1.69 (1.60–1.96) | 0.81 (0.79–0.97) | 1.87 (1.68–1.99) | 0.88 # | 1.80 # | 0.92 (0.84–1.04) | 2.15 (1.90–2.26) | 1.02 (1.01–1.11) | 2.06 (1.87–2.16) | 0.98 (0.83–1.11) | 2.14 (2.02–2.30) | 1.06 # | 2.14 # |
| Factor X | n=127 [0] | | n=58 [0] | | n=31 [1] | | n=71 [0] * | | n=54 [0] * | | n=66 [0] | | n=39 [0] * | |
| | 0.75 (0.66–0.82) | 1.25 (1.23–1.36) | 0.82 (0.75–0.90) | 1.35 (1.26–1.40) | 0.82 # | 1.43 # | 0.76 (0.62–0.88) | 1.41 (1.31–1.62) | 0.74 (0.69–0.86) | 2.02 (1.75–2.11) | 0.72 (50.9–0.82) | 1.48 (1.37–1.68) | 0.82 # | 1.41 # |
| Factor XI | n=128 [0] | | n=58 [0] | | n=31 [0] | | n=71 [1] | | n=54 [0] | | n=66 [0] | | n=39 [0] | |
| | 0.52 (0.45–0.57) | 1.80 (1.51–1.97) | 0.58 (0.57–0.61) | 1.66 (1.43–1.72) | 0.50 # | 1.73 # | 0.60 (0.53–0.66) | 1.40 (1.34–1.44) | 0.54 (0.53–0.63) | 1.97 (1.46–2.00) | 0.43 (0.28–0.56) | 1.76 (1.54–1.83) | 0.62 # | 1.71 # |
| Factor XII | n=127 [0] | | n=55 [0] | | n=28 [0] | | n=72 [0] | | n=54 [0] | | n=63 [0] | | n=39 [0] | |
| | 0.81 (0.58–0.85) | 1.87 (1.81–2.65) | 0.66 (0.53–0.90) | 2.22 (1.93–2.26) | 0.92 # | 2.18 # | 0.88 (0.86–1.03) | 1.97 (1.84–2.06) | 0.86 (0.81–1.04) | 2.10 (1.98–2.14) | 0.77 (0.72–0.88) | 2.17 (1.89–2.30) | 0.97 # | 2.20 # |

# Factor VII

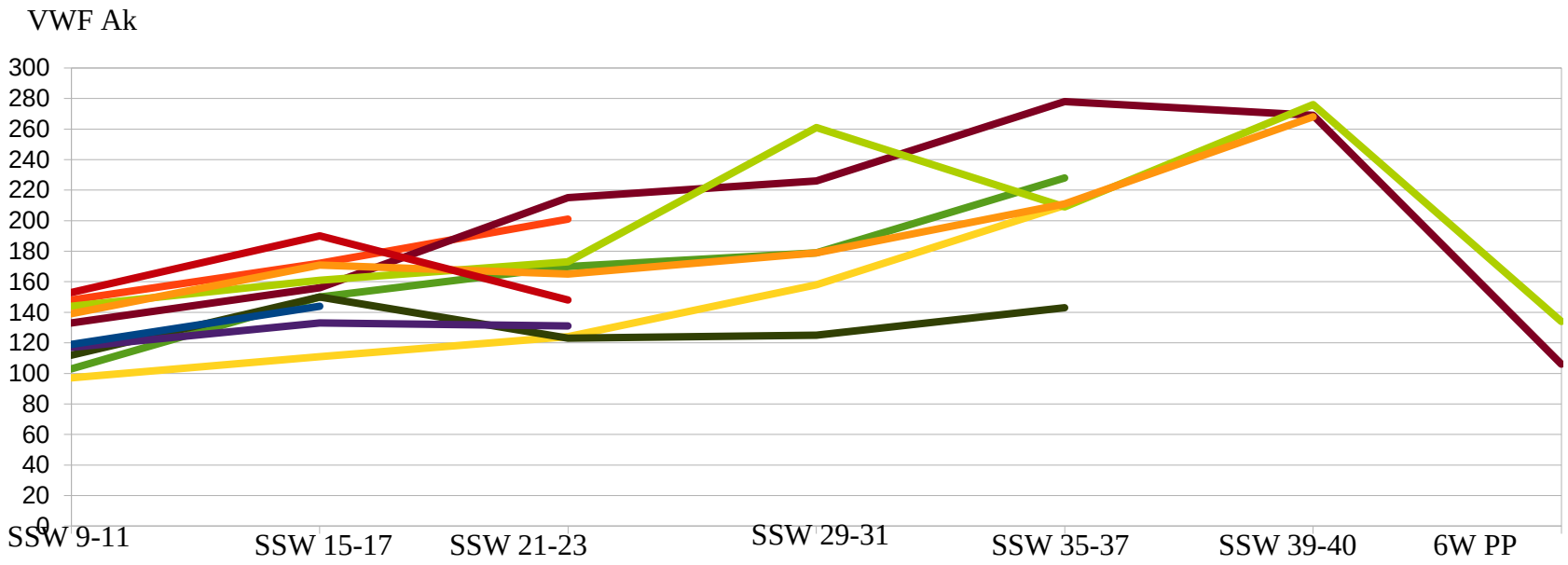
Faktor VII



# Factor VIII


Faktor VIII
clotting
160
140
120
100
80
60
40
20
0
SSW 9-11
SSW 15-17
SSW 21-23
SSW 29-31
SSW 35-37
SSW 39-40
6W PP

# Von Willebrand Activity



dr. rott
dr. halimeh
dr. kappert

gerinnungs
zentrum
rhein-ruhr

# Treatment of PPH

Dr. med. Susan Halimeh

**TABLE 4. Recommendations for the prophylactic treatment of women with inherited bleeding disorders***

| Deficiency | Management |
|---|---|
| VWD | |
| Type 1 | TXA, DDAVP |
| Type 2 | TXA, VWF concentrates, DDAVP in responders |
| Type 3 | TXA, VWF concentrates |
| Afibrinogenemia and hypofibrinogenemia | Replacement therapy according to availability (fibrinogen concentrate, cryoprecipitate, FFP†) and volume status |
| Dysfibrinogenemia | Women with dysfibrinogenemia are also at risk of both postpartum thrombosis and PPH. Postpartum management of these women should be individualized based on their fibrinogen level as well as personal and family history of bleeding and thrombosis. Postpartum thromboprophylaxis in these patients also requires individualized management. |
| FII | PCCs to maintain FII level >20%-30% |
| FV | FFP† (increase FV level to >15%-25%) |
| FV plus FVIII | FV >15%-25%; FVIII >50% (combination of DDAVP or FVIII concentrate and FFP†) |
| FVII | rFVIIa or nonactivated plasma-derived FVII concentrate (15-30 μg/kg) for women with FVII level of <10%-20% hemostatic level for uterine bleeding OR surgery may be higher (clinical observation) |
| FX | Replacement therapy during labor and delivery (FX concentrate or PCC as available) in women with FX levels of <10%-20%. In women with FX level >10%-20% and no significant bleeding history, a conservative approach could be adopted. |
| FXI | Prophylactic treatment with TXA should be considered after delivery up to 2 weeks. For those with a bleeding phenotype and severe deficiency of FXI should receive FXI concentrate if available, otherwise FFP†. Prophylactic treatment with TXA should be considered after delivery for up to 2 weeks. The concomitant use of TXA and FXI concentrates should be avoided due to increased thrombogenicity |
| FXIII | The incidence of PPH in women with FXIII deficiency is not known. Successful pregnancy in women with FXIII subunit A deficiency is generally only achieved with replacement therapy throughout pregnancy (using FXIII concentrate); a level >10%-20% during pregnancy should be considered. |
| Carriers of hemophilia | FVIII carrier: TXA, DDAVP, FVIII replacement (recombinant or plasma derived)<br>F IX carrier: TXA, F IX replacement (recombinant or plasma derived) |

* It is possible that a patient may deliver where no products but standard blood products are immediately available for an unexpected bleed. In such cases, FFP is used as a second choice. Cryoprecipitate can also be used as a second choice in carriers of hemophilia, VWD, and fibrinogen and FXIII deficiency. Adapted from Peyvandi et al.,[34] Grade 3-I.

† Virus inactivated when available.

DDAVP = desmopressin; PCC = prothrombin complex concentrate.

## TABLE 7. Approaches to prevention and management of PPH

| Stage | Patient status | Treatment |
|---|---|---|
| Prevention of PPH | Woman with high risk of PPH (Grade 1-I) *(bleeding disorder, placenta previa, twins, antepartum hemorrhage)* | Germany:[35] oxytocin—3 IU bolus IV following cord clamp. Second bolus of 3 IU oxytocin if required<br>France:[56] oxytocin—5 IU IV following cord clamp<br>United Kingdom:[10] oxytocin—5 IU IM (vaginal delivery) or 5 IU IV (cesarean delivery) NB. Some centers have reverted to using Syntometrine after observing an increase in the prevalence of PPH<br>Misoprostol*—800 μg PR<br>TXA (according to national guidelines) |
| | Woman not at high risk or with no evidence of bleeding (Grade 1-I) | Uterotonic therapy according to country-specific guidelines, e.g., Syntometrine<br>France:[56] oxytocin—5 IU IV following cord clamp, with 10 IU IV infusion (maximum 30 IU in 30 min) |
| First-line treatment | All women who develop hemorrhage postpartum (Grade 1-I) | Assess clinical response with uterotonic agents (Grade 1-I)<br>IV infusion and IM bolus of oxytocin (combination with prostaglandins considered dependent on local practice†): e.g., Syntocinon (40 IU over 4 hr); ergometrine (500 mg IV): misoprostol (800 μg PR)<br>*Country-specific guidelines:*<br>France:[56] oxytocin infusion (30 IU/30 min) followed by initial Sulprostone infusion (500 μg/1 hr) then 500 μg/6-12 hr depending on the rate of bleeding<br>Germany:[35] oxytocin infusion (10-40 IU oxytocin/500-1000 mL crystalloid solution) depending on uterine tone<br>Persistent bleeding: stop oxytocin infusion. Begin Sulprostone (500 μg/500 mL crystalloid solution) IV 1.7 μg/min (max rate 8.3 μg/min, max dose 1500 μg in 24 hr) |
| Second-line treatment | Failure to stop bleeding with uterotonics | *Nonsurgical measures:*<br>Coagulation screen<br>TXA (Grade 1-II)<br>Fibrinogen supplementation (Grade 3-I)<br>Blood product transfusion<br>*Obstetric assessment and surgical intervention:*<br>Bimanual compression<br>Balloon tamponade/B-Lynch sutures (the choice depends on the mode of delivery)<br>Packing the uterus<br>Uterine artery embolization |
| Third-line treatment | Failure to stop bleeding with first operative procedure | B-Lynch sutures if not yet performed<br>Hysterectomy<br>*Nonsurgical:*<br>rFVIIa‡ (Grade 3-I) |

* The consensus panel agrees that when considering the benefits safety profile of misoprostol alongside the benefits of its physiologic effects it is reasonable to administer prophylactically in women at high risk of PPH.

† Route of administration and dose varies between countries.

‡ Administration is off-label and the group did not reach consensus regarding its role in management of PPH.

IU = international unit; IM = intramuscular; PR = per rectal; U = unit.

**TABLE 7. Approaches to prevention and management of PPH**

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|---|---|---|
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| | Woman not at high risk or with no evidence of bleeding (Grade 1-I) | Uterotonic therapy according to country-specific guidelines, e.g., Syntometrine<br>France:[56] oxytocin—5 IU IV following cord clamp, with 10 IU IV infusion (maximum 30 IU in 30 min) |
| First-line treatment | All women who develop hemorrhage postpartum (Grade 1-I) | Assess clinical response with uterotonic agents (Grade 1-I)<br>IV infusion and IM bolus of oxytocin (combination with prostaglandins considered dependent on local practice), e.g., Syntocinon (40 IU over 4 hr); ergometrine (500 mg IV): misoprostol (800 µg PR)<br>*Country-specific guidelines:*<br>France:[56] oxytocin infusion (30 IU/30 min) followed by initial Sulprostone infusion (500 µg/1 hr) then 500 µg/6-12 hr depending on the rate of bleeding<br>Germany:[35] oxytocin infusion (10-40 IU oxytocin/500-1000 mL crystalloid solution) depending on uterine tone<br>Persistent bleeding: stop oxytocin infusion. Begin Sulprostone (500 µg/500 mL crystalloid solution) IV 1.7 µg/min (max rate 8.3 µg/min, max dose 1500 µg in 24 hr) |
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* The consensus panel agrees that when considering the benefits safety profile of misoprostol alongside the benefits of its physiologic effects it is reasonable to administer prophylactically in women at high risk of PPH.
† Route of administration and dose varies between countries.
‡ Administration is off-label and the group did not reach consensus regarding its role in management of PPH.
IU = international unit; IM = intramuscular; PR = per rectal; U = unit.

Oxytoxin bolus or other uterotonic therapy and TXA

Uterotonic therapy

Coagulation screen

TXA

Fibrinogen substitution

and other obstetric interventions

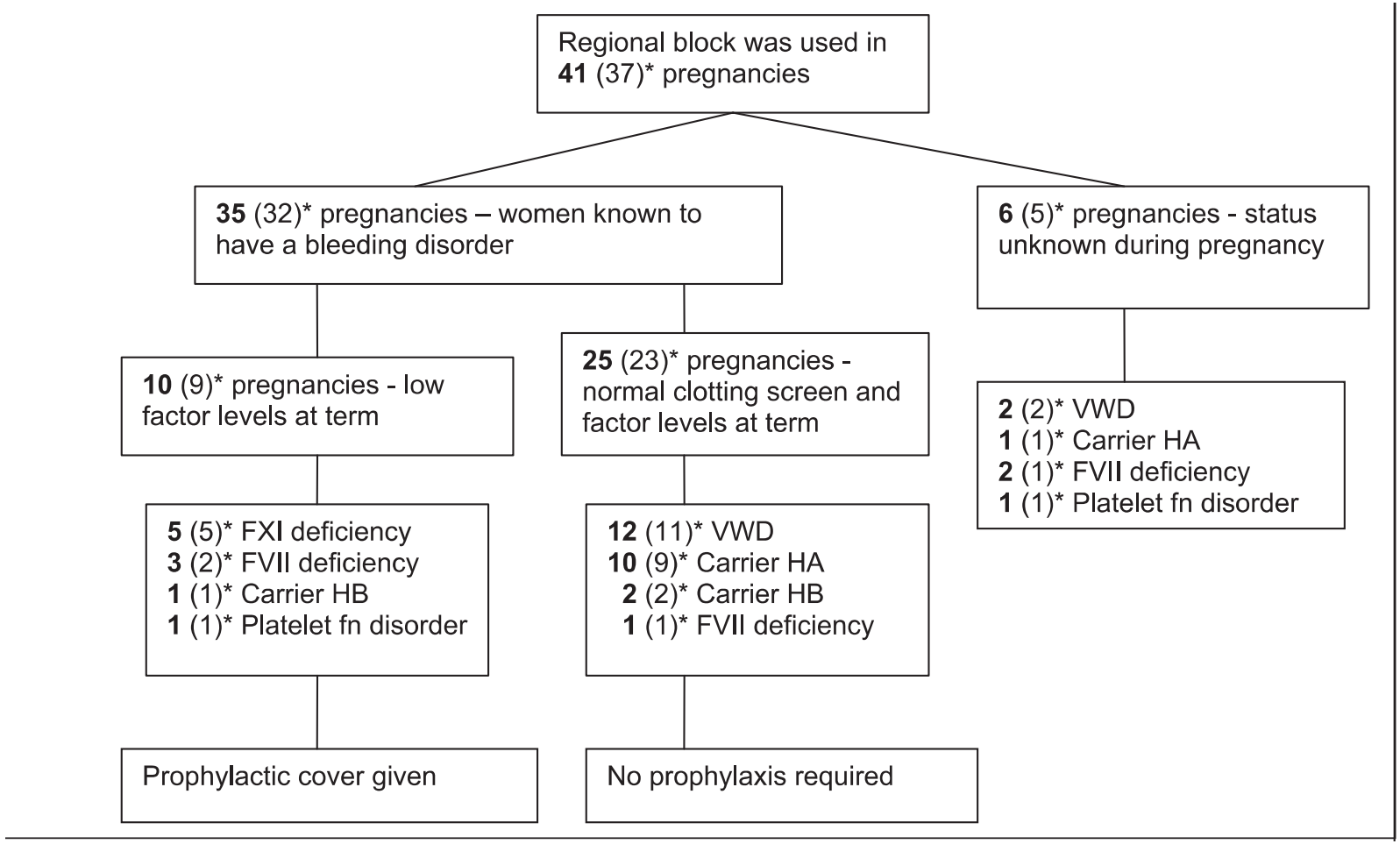
# Obstetric analgesia and anaesthesia in women with inherited bleeding disorders

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**Summary**

A retrospective review was carried out on the methods of obstetric analgesia/anesthesia used in 80 pregnancies amongst 63 women with inherited bleeding disorders (19 factor XI deficiency, 16 carriers of haemophilia, 15 von Willebrand disease, seven platelet function disorders, four factor VII deficiency, one factor VII and XI deficiency and one factor X deficiency). In 72 pregnancies, the woman was seen antenatally in a multidisciplinary clinic to discuss and plan pain relief options. Regional block was performed for 41 pregnancies. The mothers were known to have a bleeding disorder in 35 of these pregnancies. Prophylactic cover was given in 10 pregnancies prior to the insertion of regional block but not required in the remaining 25 pregnancies because the coagulation defects had spontaneously normalised at term. There were six reported adverse effects from regional block similar to that found in the general population: inadequate anesthesia/analgesia (2), bloody tap (2), hypotension and a possible dural puncture which was treated conservatively. There were no reports of long-term complications. The findings show that it is possible to offer women with inherited bleeding disorders the option of regional block provided their coagulation defects have normalised, either spontaneously during pregnancy or following adequate haemostatic cover.


Regional block was used in
**41** (37)* pregnancies
**35** (32)* pregnancies – women known to have a bleeding disorder
**6** (5)* pregnancies - status unknown during pregnancy
**10** (9)* pregnancies - low factor levels at term
**25** (23)* pregnancies - normal clotting screen and factor levels at term
**2** (2)* VWD
**1** (1)* Carrier HA
**2** (1)* FVII deficiency
**1** (1)* Platelet fn disorder
**5** (5)* FXI deficiency
**3** (2)* FVII deficiency
**1** (1)* Carrier HB
**1** (1)* Platelet fn disorder
**12** (11)* VWD
**10** (9)* Carrier HA
**2** (2)* Carrier HB
**1** (1)* FVII deficiency
Prophylactic cover given
No prophylaxis required


hand








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