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Bleeding Disorders in Pregnancy

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Conflict of Interest

Company/Organization	Role
Canadian Blood Services	Medical Consultant
Amgen	Advisory Board/Honorarium
GlaxoSmithKline	Advisory Board/Honorarium
Bayer	Local Investigator
Pfizer	Local Investigator

Overview

- Hemostatic changes in pregnancy
- Hemostatic Assessment
- Congenital Bleeding Disorders
- Immune Thrombocytopenia Purpura

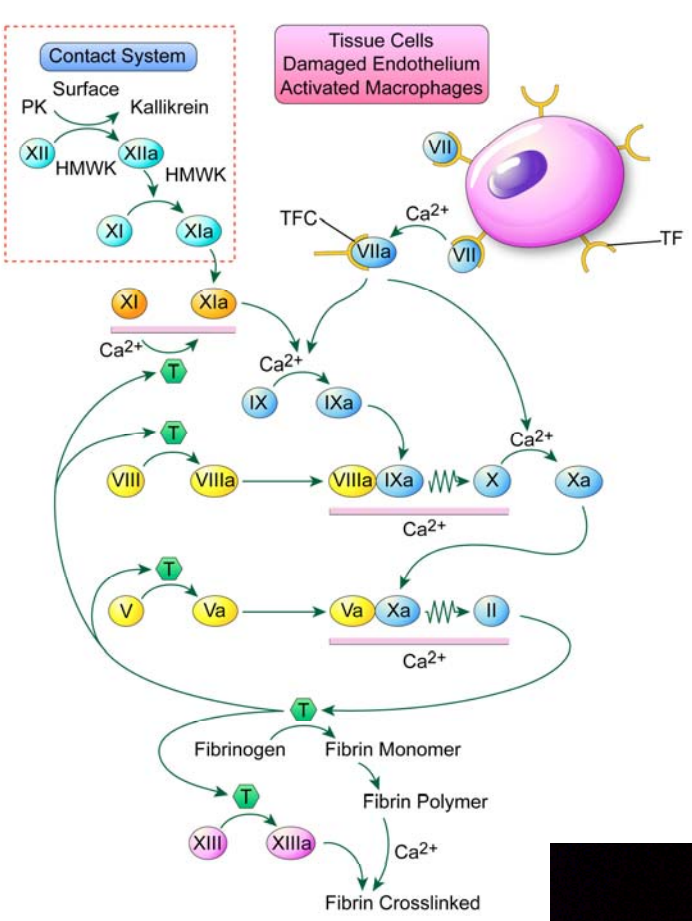
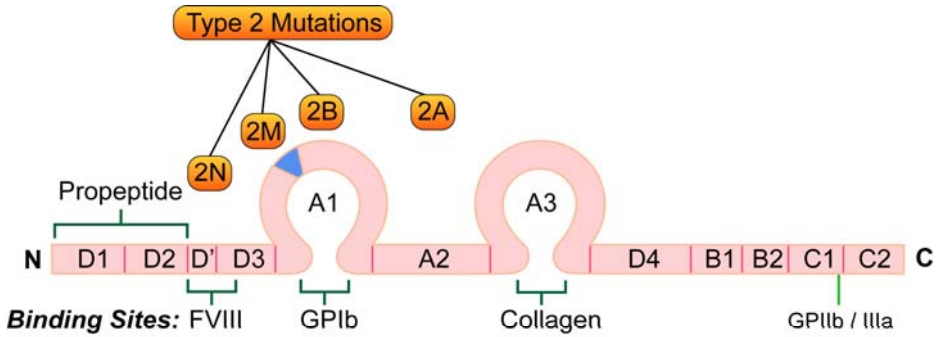
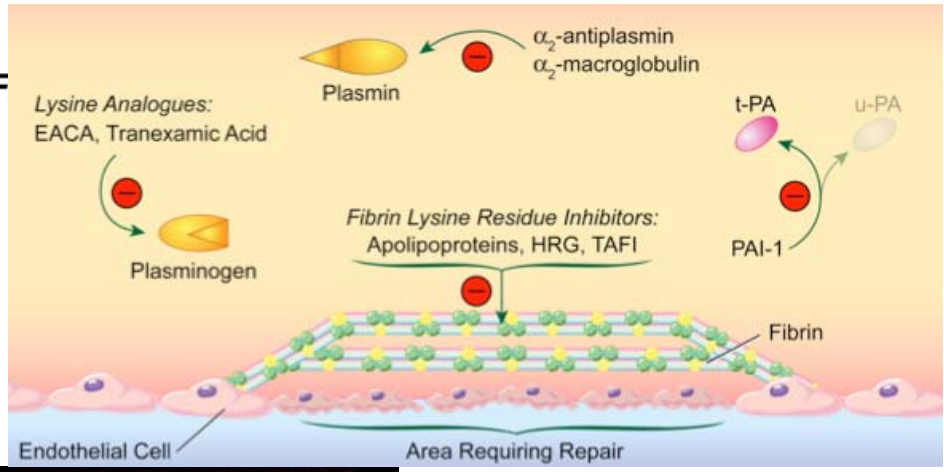
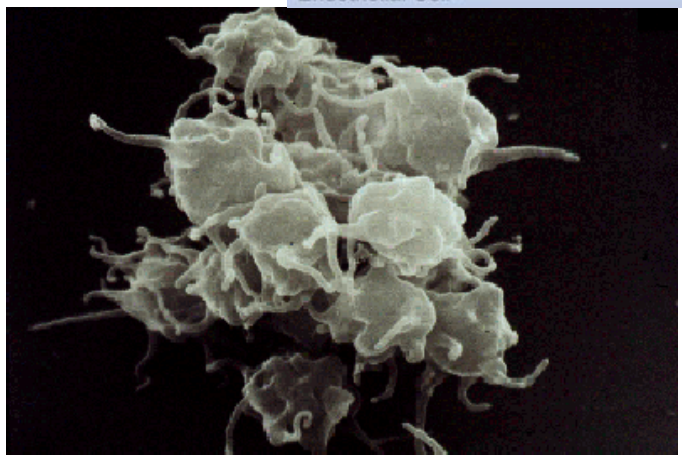


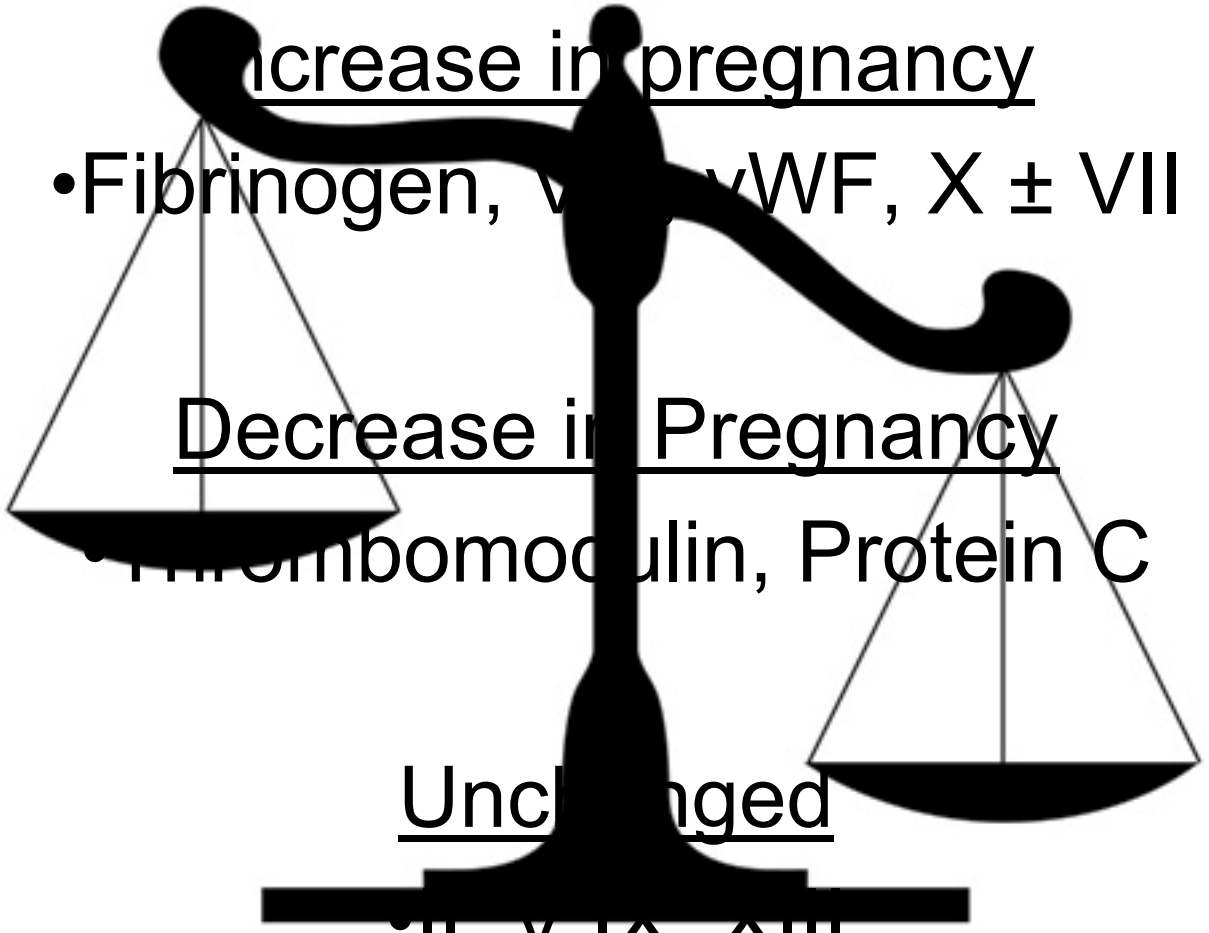
Figure 20-1 The Coagulation Cascade







Coagulation in Pregnancy



ncrease in pregnancy

•Fibrinogen, v WF, X ± VII

Decrease in Pregnancy

•Thrombomodulin, Protein C

Unch nged

•II, V IX, XIII

Bleeding History

- Menstrual history
- Spontaneous bleeding
- Hemostatic Challenges
  - Surgery
  - Dental
  - Pregnancy
- Family history
- Medications

CONDENSED MCMDM-1 BLEEDING QUESTIONNAIRE:

	Score					
Symptom	-1	0	1	2	3	4
Epistaxis	--	No or trivial (less than 5)	> 5 or more than 10'	Consultation only	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Cutaneous	--	No or trivial (< 1cm)	> 1 cm and no trauma	Consultation only	--	--
Bleeding from minor wounds	--	No or trivial (less than 5)	> 5 or more than 5'	Consultation only	Surgical hemostasis	Blood transfusion or replacement therapy or desmopressin
Oral cavity	--	No	Referred at least one	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Gastrointestinal bleeding	--	No	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytic	--
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing or packing	Blood transfusion or replacement therapy or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1 surgery	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Menorrhagia	--	No	Consultation only	Antifibrinolytics, pill use	Dilation & curettage, iron therapy, ablation	Blood transfusion or replacement therapy or desmopressin or hysterectomy
Postpartum hemorrhage	No bleeding in at least 2 deliveries	None done or no bleeding in 1 surgery	Consultation only	Dilation & curettage, iron therapy, antifibrinolytics	Blood transfusion or replacement therapy or desmopressin	Hysterectomy
Muscle hematomas	--	Never	Post trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	--	Never	Post trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system bleeding	--	Never	--	--	Subdural, any intervention	Intracerebral, any intervention

Score ≥ 4 is abnormal (Sensitivity 100% for vWD).

Bowman et al. J Thromb Haemost 2008; 6: 2062–6.

Screening for Bleeding Disorders

- CBC
- INR
- aPTT
- Fibrinogen

- vWF:antigen
- vWF:RCof
- Factor VIII
- Factor IX
- Factor XI
- Platelet aggregation
- Platelet release

Congenital Bleeding Disorders

	Inheritance	Inheritance	Hemostatic Level
Von Willebrand Disease	AD	1:1000-10,000	0.5
Platelet Disorders	Varies	1:1000	--
Hemophilia A carrier	X-linked	1:5,000	0.5
Hemophilia B carrier	X-linked	1:25,000	0.5
Factor VII	AR	1:500,000	0.1-0.2
Fibrinogen deficiency	AR	1:1,000,000	1 g/L*
Factor II	AR	1:2,000,000	0.1-0.2
Factor V	AR	1:1,000,000	0.15-0.25
Factor XI	AR	1:1,000,000	0.2-0.7
Factor X	AR	1:1,000,000	0.1-0.2
Factor XIII	AR	1:1,000,00	0.2-0.3*

Huq et al. Haemophilia 2011: 17 (S1), 20–30
Hay et al. Haemophilia 2004: 10, 593–628

Case- Type I von Willebrand Disease

- 26 year old female G1P0. 12 weeks gestational age. vWF Ag 0.38 and vWF Rcof 0.33
  - Hx of menorrhagia (7 days, change pad q1h)
  - Easy bruising and epistaxis as child
  - No other bleeding challenges
  - Mother and sister have heavy periods

Classification of von Willebrand Disease

Type	Description
1	Partial quantitative deficiency of VWF
2	Qualitative VWF defect
2A	Decreased VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers
2B	Increased affinity for platelet GPIb
2M	Decreased VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers
2N	Markedly decreased binding affinity for FVIII
3	Virtually complete deficiency of VWF

Diagnosis, Evaluation and Management of von Willebrand Disease. NHLBI 2010.

Bleeding in vWD

Table 7. Common Bleeding Symptoms of Healthy Individuals and Patients Who Have VWD

Symptoms	Normals (n = 500;[137] n= 341;[‡138] n = 88;[‡‡139] n= 60[‡‡140]) %	All types VWD (n = 264;[137] n = 1,885[141]) %	Type 1 VWD (n = 42;[†142] n = 671[136]) %	Type 2 VWD (n = 497[136]) %	Type 3 VWD (n = 66;[136] n = 385[85]) %
Epistaxis	4.6–22.7	38.1–62.5	53–61	63	66–77
Menorrhagia*	23–68.4	47–60	32	32	56–69
Bleeding after dental extraction	4.8–41.9	28.6–51.5	17–31	39	53–70
Ecchymoses	11.8–50	49.2–50.4	50	N.R.	N.R.
Bleeding from minor cuts or abrasions	0.2–33.3	36	36	40	50
Gingival bleeding	7.4–47.1	26.1–34.8	29–31	35	56
Postoperative bleeding	1.4–28.2	19.5–28	20–47	23	41
Hemarthrosis	0–14.9	6.3–8.3	2–3	4	37–45
Gastrointestinal bleeding	0.6–27.7	14	5	8	20

Diagnosis, Evaluation and Management of von Willebrand Disease. NHLBI 2010.

Diagnosis of type I vWD

1. Significant mucocutaneous bleeding symptoms
   - Epistaxis, cutaneous, oral, dental, menorrhagia
   - 2 symptoms, repeated episodes or transfusion
2. Positive family history
3. vWD:Ag and vWD Rcof > 2 SD below mean

Possible type I vWD

- Laboratory criteria without bleeding symptoms or family history

Changes in VWF levels in pregnancy

- vWF levels increase 2-3 fold
  - Gradual increase with highest levels in 2nd or 3rd trimester
  - Rare type 1 subtypes do not increase
  - Type 2 variable increases
- Check baseline levels and prior to any procedures
- Check levels at 28-32 weeks

Antenatal issues

- Pregnancy Loss
  - Only factor XIII and fibrinogen deficiency clearly associated with pregnancy loss (implantation)
  - ? Increased rate in vWD (33%) in one study of 84 patients
- Antepartum Hemorrhage
  - No increase in case control sutdy of 114 vWD and hemophilia carriers
  - U.S. database of 4000 vWD patients reported an odds ratio of 10.2 for antenatal but not increase in more serious sequelae.

Sibonin SM. Haemophilia 2009; 15: 1291–9.
James AH. J Thromb Haemost 2007; 5: 1165–9.

Delivery in Bleeding Disorder Patients

- If levels normalize or replacement factor then no maternal advantage to C-section
  - Type I vWD, hemophilia carriers
  - Avoid prolonged labour, fetal blood sampling, vaccum extraction, forcep delivery.
- Mode of delivery may be more related to fetal risk
- If levels do not increase then advantage to planned delivery
  - Induction or C-section ensure pre-emptive factor decision

Huq. Haemophilia 2011: 17(S1):20-30
Lee. Haemophilia 2006: 12:301-306
BCSH Guidelines. Management of the Fetus and Neonate in Haemophilia, 2011

Fetal risk with vaginal delivery with severe bleeding disorders

- Intracranial and extracranial hemorrhages account for 40% of neonatal bleeds.
- Higher risk with vaccum extraction (5.9%) compared to regular vaginal delivery (2.3%) in hemophiliac newborns

Ljung. Acta Pediatr 1994: 83: 609.

Spinal anesthesia

- Safe with normal coagulation factor levels
  - Document levels in 3rd trimester for vWD and hemophilia carriers A
  - Factor replacement before insertion and removal
- Recent systematic review of 507 cases of regional anesthesia in vWD, hemophilia and ITP
  - 1 bleeding event in nondiagnosed infant

Choi. Anesth Analg. 2009 Aug;109(2):648-60.

Postpartum Hemmorhage

- Primary PPH (within 24 hrs) in 4-6% of all pregnancies
- Secondary PPH (24 hrs – 6 wks) in 1-3% of all pregnancies
  - Levels start to decrease within 3 days with nadir at 7-21 days
- vWD has increased risk of PPH
  - Odds ratio of 3.3

Postpartum Management

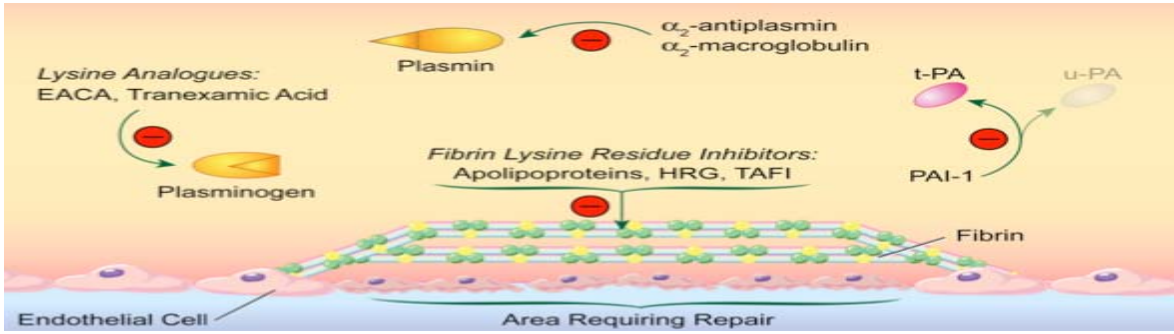
- Replace factor as available
  - 3 to 4 days for vaginal delivery
  - 3 to 7 days for Cesarean section
- Active management of labour
  - Uterotonics
  - Cord traction to deliver placenta
- DDAVP and cyklokapron

DDAVP

- Release of vWF and factor VIII from endothelial stores
- Increase levels 2-5 fold in most patients
- Tachyphylaxis after 2-3 doses
  - Combine with anti-fibrinolytics
- Does not affect V1 uterine muscle receptors
- Safe early in pregancy and peripartum
  - Recent systematic review of 30 studies (216 patients)
- Risk of hyponatremia if fluid intake not controlled
  - Increased with use of oxytocin at time of delivery

Trigg. Haemophilia. 2012 Jan;18(1):25-33.

Anti-Fibrinolytics



- Bind to plasminogen to prevent fibrinolysis
- Useful for all bleeding disorders or normal patients with post-partum bleeding
- May be used for ante-natal bleeding
- Dose of 10 mg/kg IV or 25/mg/kg oral for 5-10 days
- Combined with factor replacement or DDAVP

Anti-Fibrinolytics and Thrombosis

- 2 RCTs (453 patients) of patients without bleeding disorders showed reduction in blood loss. No report of thrombosis
- No increase in thrombosis in high risk surgery
- No increase in thrombosis in CRASH-2 study

Table 1: Effect of TXA

Events	RR	95% CI
Myocardial infarction	0.96	0.48-1.90
Stroke	1.25	0.47-3.31
Deep venous thrombosis	0.77	0.37-1.61
Renal failure	0.73	0.16-3.32

Peidisitis. Expert Opin Pharmacother 2011; 12: 503
Henry. Cochrane Database Syst Rev 2007
Novikova. Cochrane Database Syst Rev 2011

Factor Replacement

Bleeding Disorder	Replacement Product
Hemophilia A	Recombinant Factor VIII
Hemophilia B	Recombinant Factor IX
vWD	Humate P (plasma derived vWD/VIII) Willate (plasma derived vWD/FVIII) *[Recombinant vWD]*
Fibrinogen	Cryoprecipitate Plasma derived fibrinogen concentrate
Factor II, X	Frozen Plasma Prothrombin Concentrate Complex
Factor V	Frozen Plasma
Factor VII	Plasma derived factor VII Prothrombin Concentrate Complex Recombinant activated Factor VII
Factor XI	Plasma derived factor XI concentrate Frozen Plasma
Factor XIII	Cryoprecipitate Plasma derived factor XIII concentrate Recombinant factor XIII concentrate

Case 2 - New Thrombocytopenia

27 year old G2P0 female

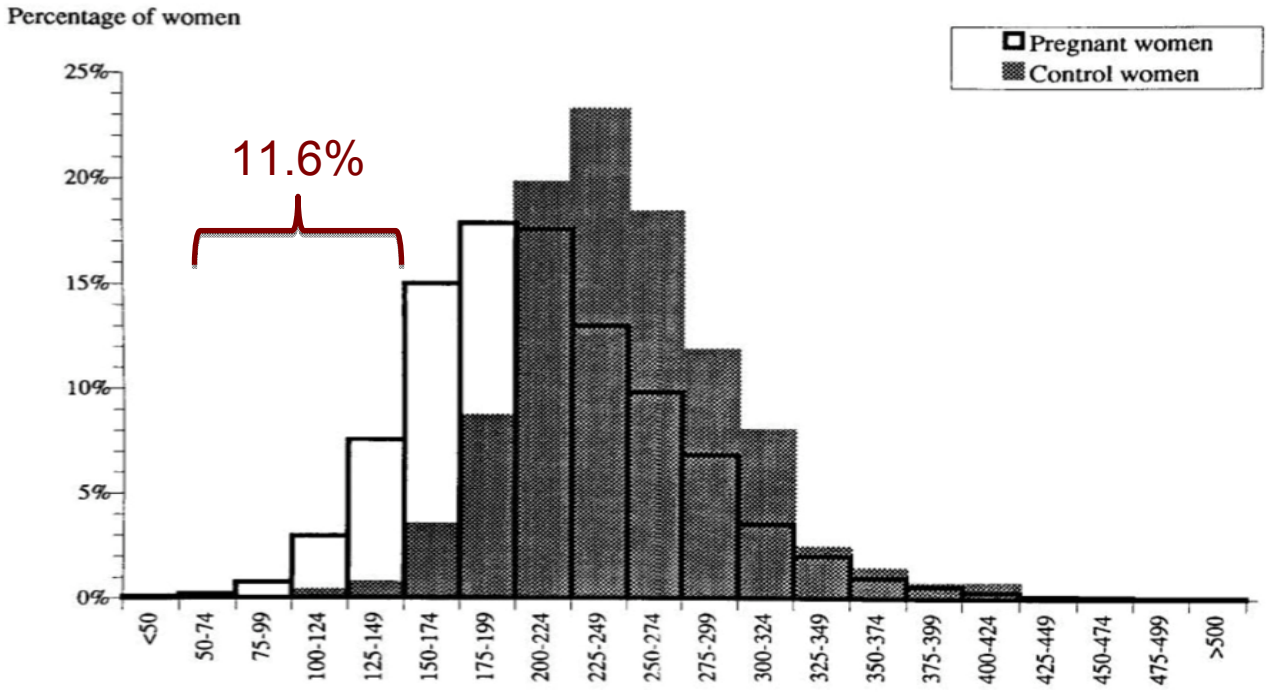
- 38 wks gestational age with platelet count 60 x 10^9/L
- Platelets normal in first trimester but decreased to 83 x 10^9/L at 28 wks
- Normal blood film, liver enzymes and LDH.

- Past medical hx: ectopic pregnancy, eczema, asthma

- No family history of thrombocytopenia

Defining Thrombocytopenia

- 6770 pregnant patients in 3rd trimester and 287 controls



	Mean Platelet Ct	2.5th Percentile
Pregnant	213	116
Non-Pregnant	248	164

Boehlen, Obstet Gynecol. 2000 Jan;95(1):29-33.

Thrombocytopenia in pregnancy

1. Gestational thrombocytopenia (75% of cases)
   - 4-8% of pregnancies
   - Usuallly occurs in latter half of pregnancy
2. Hypertensive disorders associated with thrombocytopenia (20% of cases)
   - Preeclampsia/HELLP
   - Occurs late in pregnancy and plat ct > 100 x 10^9/L
3. ITP in pregnancy (3-4% of cases)
   - 'De novo' presentation (1/3) or 'known' history (2/3)
   - 1:10000 deliveries
4. Other
   - AFLP, TTP, DIC,
   - Congenital thrombocytopenia, type IIb vWD

Burrows, Kelton. (1988) NEJM, 319, 142–145.
Burrows, Kelton. (1990). AJOG, 162, 731–734.
Burrows, Kelton. (1992). Obstetrics and Gynaecology,.

Thrombocytopenia in pregnancy

- 6-10% of pregnancies

Pregnancy-specific	Not pregnancy-specific
Gestational thrombocytopenia	Primary immune thrombocytopenia
Preeclampsia/Eclampsia	Secondary immune thrombocytopenia
HELLP syndrome	Viral infection (HIV, Hep C, CMV, EBV, ot hers)
Acute fatty liver	Autoimmune disorders (SLE, others)
	Antiphospholipid antibodies
	Thrombotic microangiopathies
	*Thrombotic thrombocytopenic purpura**
	*Hemolytic-uremic syndrome**
	Disseminated intravascular coagulation (DIC)
	Bone marrow (MDS, myelofibrosis)
	Nutritional deficiencies
	Drugs
	*Type IIB vWD induced thrombocytopenia**
	Inherited thrombocytopenia (May-Hegglin, etc)
	Hypersplenism

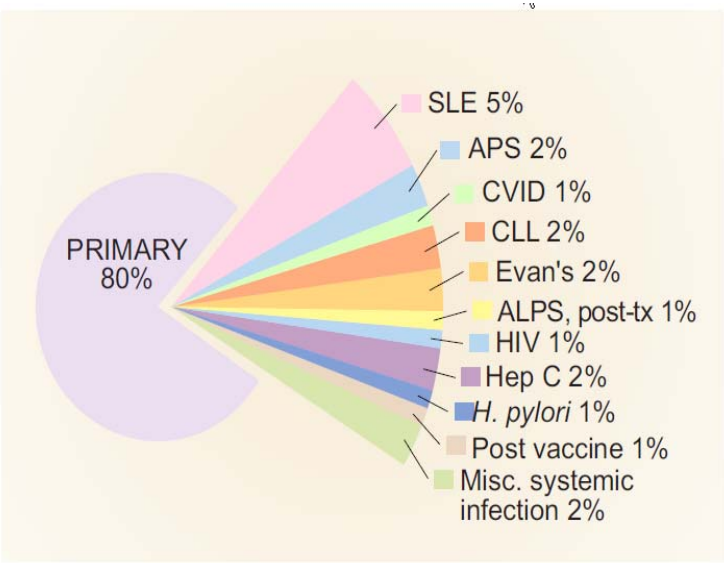
McCrae. Hematology 2010; 397:402.

Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group

What is ITP?

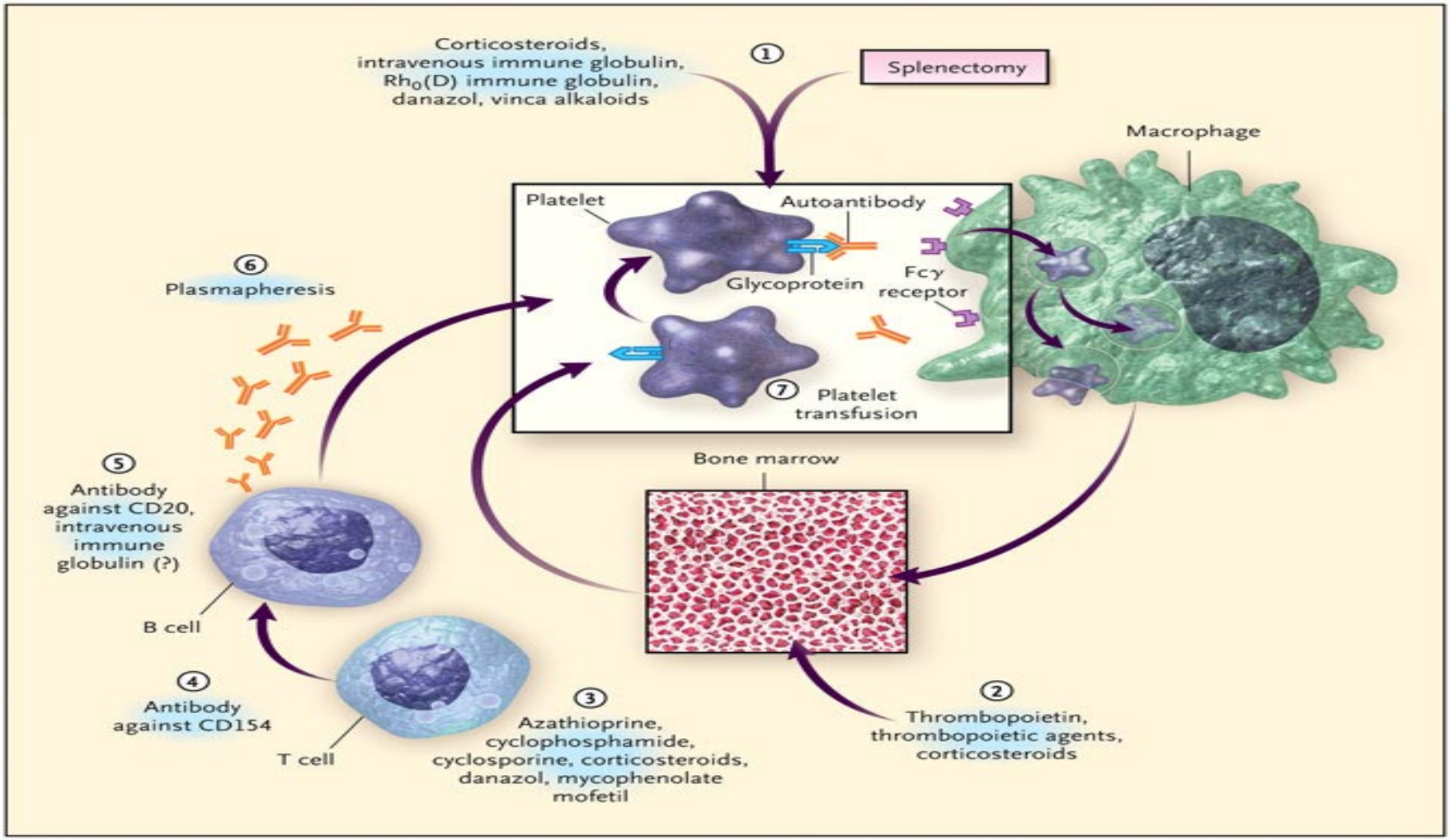
Immune Thrombocytopenia Purpura

- Primary
  - Platelet count < 100 x 10^9/L
  - Absence of other disorders
  - No specific laboratory tests
- Secondary
  - All other forms of ITP



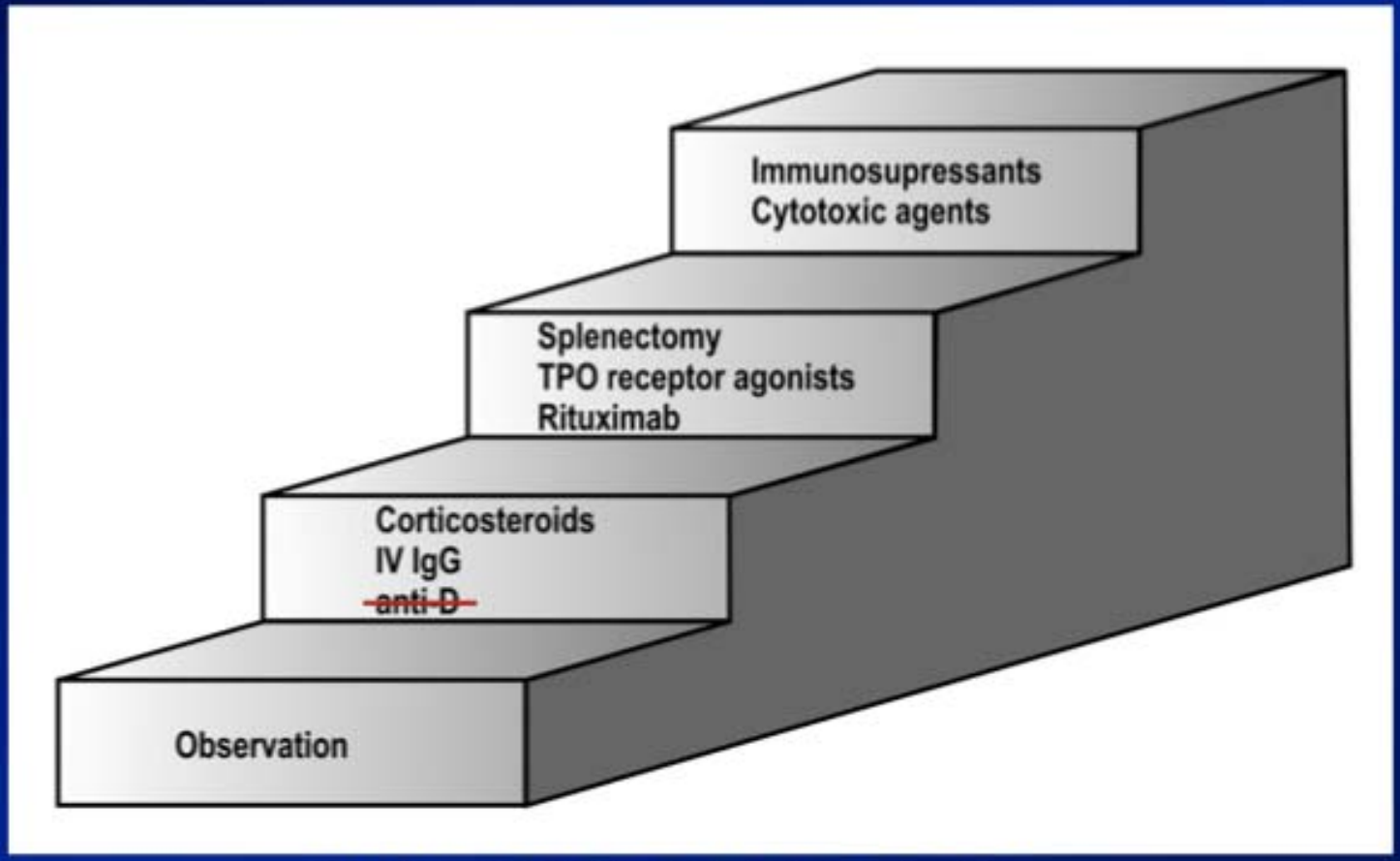
Rodrigheiro. Blood 2010; 113: 2386.

Treatment of ITP in 2012



Bromberg M. N Engl J Med 2006;355:1643-1645

TREATMENT OF ITP



STAIRCASE APPROACH

Minimal experience: dapsone, colchicine, vincristine

Arnold, Kelton (2007)

Courtesy of John Kelton

Treatment of ITP in pregnancy

1. Prevent maternal bleeding complications
   - Platelets > 20-30 x 10^9/L considered safe even in 3rd trimester
2. Prevent fetal and neonatal bleeding complications
   - ? Effect of treatment on baby
3. Platelet count greater that 50-70 x 10^9/L for delivery
4. Allow for epidural anesthesia
   - Platelets > 70-80 x 10^9/L

Provan 2010. Blood 115: 167.
Neunert 2011. 117: 4190.

Case 2 - continued.

Delivery

IVIG

Date/Time	Today	Description	Reg C	Perf C	Result	Unit
						--Top of List --
Sep 05 2012 16:44		PLAT	G	C	135	10^9/L
Jul 04 2012 14:51		PLAT	G	C	133	10^9/L
May 03 2012 15:51		PLAT	C	R	155	10^9/L
Apr 26 2012 14:52		PLAT	R	R	104	10^9/L
Apr 22 2012 08:41		PLAT	C	C	49	10^9/L
Apr 21 2012 09:46		PLAT	C	C	46	10^9/L
Apr 20 2012 12:35		PLAT	C	C	44	10^9/L
Apr 18 2012 10:27		PLAT	R	R	52	10^9/L
Apr 15 2012 08:30		PLAT	G	G	57	10^9/L
Apr 13 2012 11:14		PLAT	G	G	59	10^9/L

- Treated with IVIG 1g/kg
  - Response within 24 - 48 hrs with
  - Maximum platelet count ~ 7 days
  - Average duration of response 3-4 weeks

Retrospective study of ITP in Pregnancy

- 119 pregnancies
  - 70% with known ITP
- 22% with moderate to severe bleeding
- 31% required treatment
  - 20 IVIG
  - 8 prednisone
  - 7 IVIG and prednisone

Webert. Blood 2003; 102: 1306.

Response to therapy

Table 1. Response of obstetric patients with ITP to treatment

Treatment	Total no. pregnancies	No. in CR	No. in PR	No. with NR
No treatment	82	NA	NA	NA
All treatments	37	6	11	9
Corticosteroids	8	1	2	1
IV IgG	20	4	7	5
Corticosteroids and IV IgG	7	1	1	3
Corticosteroids, IV IgG, and anti-D	1	0	0	0
Corticosteroids and anti-D	1	0	1	0

Webert. Blood 2003; 102: 1306.

Spinal Anesthesia in ITP

- Platelet count threshold of 50-80 x 10^9/L recommended
  - BCSH Transfusion guideline > 50 x 10^9/L
  - BCSH ITP guideline > 50 x 10^9/L
- 2 Retrospective reviews showed no bleeding complications
  - 30 patients with platelet count 69-98 x 10^9/L
  - 16 patients with platelet count < 75 x 10^9/L

Belin. Anesth Anal 1997: 85:385

Webert. Blood 2003; 102: 1306.

Case 3 – Refractory ITP

- 24 year old G2P1 female from Morrocco with ITP
  - Diagnosed 2005.
  - Platelet count approx 30-40 x 10^9/L in 1st pregnancy
    - No response to steroids
  - Unplanned pregnancy
  - Platelet count < 10 x 10^9/L with heamturia
  - No response to IVIG and Decadron
  - Splenectomy at 15 weeks

Treatment of ITP in Pregnancy

First Line

- Prednisone
  - 20-50 mg/d
- Intravenous Immunoglobulin
  - 1 g/kg x 1-2 days

Second Line

- Prednisone and IVIG
- Methylpredinisilone

Third Line

- Splenectomy
- Anti D globulin
  - 50-75 mcg/kg
- ? Rituximab
- ? Azathioprine

Case 3 – continued

- Splenectomy at 15 weeks
  - Platelet count increased to 28 but < 10 x 10^9/L
- Admitted for Methylprednisilone 500 mg IV x 2 days and IVIG 2 g/kg
  - Platelets increased to 200 x 10^9/L
- Required IVIG q 1-2 wks.
- Unable to wean off steroids
- Platelet maintained about 20-30 x 10^9/L
- Still birth at 38 weeks after decreased fetal mvmt

  Placental infarcts and retrommemb hemorrhage

Case 3 - continued

- Husband and wife express wish to have another child.
  - ? Optimal management
    - IVIG/prednisone
    - Preconception treatment with Rituxan

Systematic Review: Efficacy and Safety of Rituximab for Adults with Idiopathic Thrombocytopenic Purpura

Table 2. Overall, Complete, and Partial Platelet Count Response after Treatment with Rituximab in Adults with Idiopathic Thrombocytopenic Purpura according to Studies Enrolling at Least 5 Patients Each*

Platelet Count Response, × 10^9 cells/L	Pooled Estimate (95% CI), %	Contributing Reports (Patients), *n* (*n*)
Overall response (>50)	62.5 (52.6–72.5)	19 (313)
Complete response (>150)	46.3 (29.5–57.7)	13 (191)
Partial response (50–150)	24.0 (15.2–32.7)	16 (284)

Table 3. Time to Response, Response Duration, and Follow-up of Patients with Idiopathic Thrombocytopenic Purpura Treated with Rituximab*

Variable	Median	Interquartile Range	Range	Contributing Reports (Patients), *n* (*n*)
Time to response, *wk*	5.5	3.0–6.6	2.0–18.0	6 (123)
Response duration, *mo*	10.5	6.3–17.8	3.0–20.0	16 (252)
Follow-up, *mo*	9.5	6.0–21.3	2.0–25.0	10 (187)

Arnold. Ann Int Med 2007; 146:25-33.

Rituxan in ITP

- Increased response rate when combined as initial treatment for ITP
- Refractory / relapsed ITP
  - Response rate 50-60%
  - Median duration 10½ months

Arnold. Ann Int Med 2007; 146:25-33.

Rituxan in Pregnancy

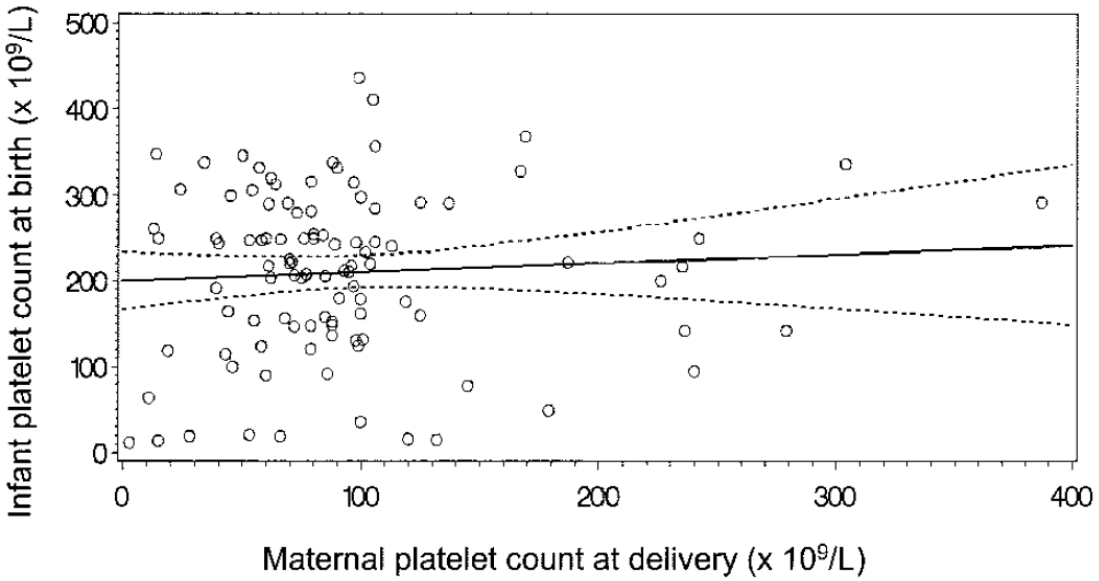
- Category C medication
- T ½ of 18-22 days
- Use prior to or during 231 pregnancies
  - 90 live births
  - 11 infants with B lymphocyte depletion lasting up to 6 months
  - 4 neonatal infections

Case 4 – Neonatal thrombocytopenia

33 yo female G2P1 with ITP. APLA negative.

- Responded to steroids at time of diagnosis
- First pregnancy required steroids in 1st trimester for vaginal bleeding and plat ct of 26
- Platelets stable at 75 in 3rd trimester. No response to steroids.
- No epidural.
- Baby had platelet count <10.
  - Treated with IVIG and platelet transfusion.
  - Resolved after 3 months

Neonatal platelet counts in ITP



Platelets	< 20 x 10^9/L	20-50 x $10^{9/L}$	50-150 x 10^9/L	> 150 x 10^9/L
% infants	5.5%	4.6%	18.3%	71.6%

Webert. Blood 2003; 102: 1306.

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Case 4 - Continued

Six months later ….

- Pregnant again.
- Platelets < 20 x 10^9/L at 12 weeks
  - No response to steroids.
  - Good response to IVIG.
  - Subsequent dose of IVIG at 20 weeks.
- Repeat testing for platelet specific antibodies negative.
- At 24 weeks, weekly treatment with IVIG for fetal platelet count.
- Neonatal platelet count 44 x 10^9/L

Neonatal Alloimmune Thrombocytopenia

- Neonatal thrombocytopenia secondary to maternal anti-platelet antibodies (i.e. anti-Pla1 or anti-HPA 1a)
- If previously affected infant
  - Standard treatment is IVIG 1-2 mg/kg IV weekly +/- steroids
  - Higher platelet count and decreased bleeding compared to sibling cohorts.

Conclusions

- Coagulation disorders affecting pregnancy are rare but regular events
- Screening by history and basic lab tests will identify most cases
- Specific therapy can avoid most maternal and fetal complication
  - Specialized treatment centres
  - Targeted therapy
  - Use of antifibrinolytics