Haematology in pregnancy

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Learning outcomes

By the end of this lecture, students will be better able to:

- Describe the normal changes in blood parameters that occur during pregnancy
- Distinguish normal gestational changes from pathological changes
- Discuss risk factors, prevention and treatment of venous thromboembolic disease in pregnancy
- Demonstrate awareness of role (if any) of prothrombotic disorders in pregnancy complications
- Appreciate major causes of postpartum haemorrhage and disseminated intravascular coagulation syndrome.
- Explain the role of maternal testing in preventing and anticipating fetal disorders

Haematology in pregnancy

- Blood count changes
  - Thrombocytopenia in pregnancy
- Coagulation changes
  - Thromboembolic disease
  - Complications of pregnancy
  - DIC syndromes
- Haemoglobinopathy
  - Haemoglobinopathy screening
  - Sickle cell disease and pregnancy
- Immune disorders

The full blood count in pregnancy

- Mild anaemia
  - Red cell mass rises (120 -130%)
  - Plasma volume rises (150%)
- Macrocytosis
  - Normal
  - Folate or B12 deficiency
- Neutrophilia
- Thrombocytopenia
  - increased platelet size

= net dilution

Blood: the demands of pregnancy

- Iron requirement
  - 300mg for fetus
  - 500mg for maternal increased red cell mass
  - RDA 30mg;
  - Increase in daily iron absorption:1-2mg to 6mg
- Folate requirements increase
  - Growth and cell division
  - Approx additional 200mcg/day required
- Iron deficiency→ IUGR, prematurity, PPH
- 5% of pregnancies have blood loss >1 litre at delivery.

IUGR = intrauterine growth restriction

Iron and folate supplements in pregnancy

- WHO recommends 60mg Fe +400mcg folic acid daily during pregnancy
- Cochrane review
  - Fe/Folate supplements had no effect on measures of maternal or fetal outcome
  - Maternal Hb higher, Fe reserves higher, fetal ferritin higher

Iron and folate supplements in pregnancy: RCOG recommendations

- Folic acid
  - Advise reduces risk of neural tube defects
  - Supplement before conception and for ≥ 12 weeks gestation
  - Dose 400µg / day
- Iron
  - No routine supplementation

Advice will vary depending on incidence in community

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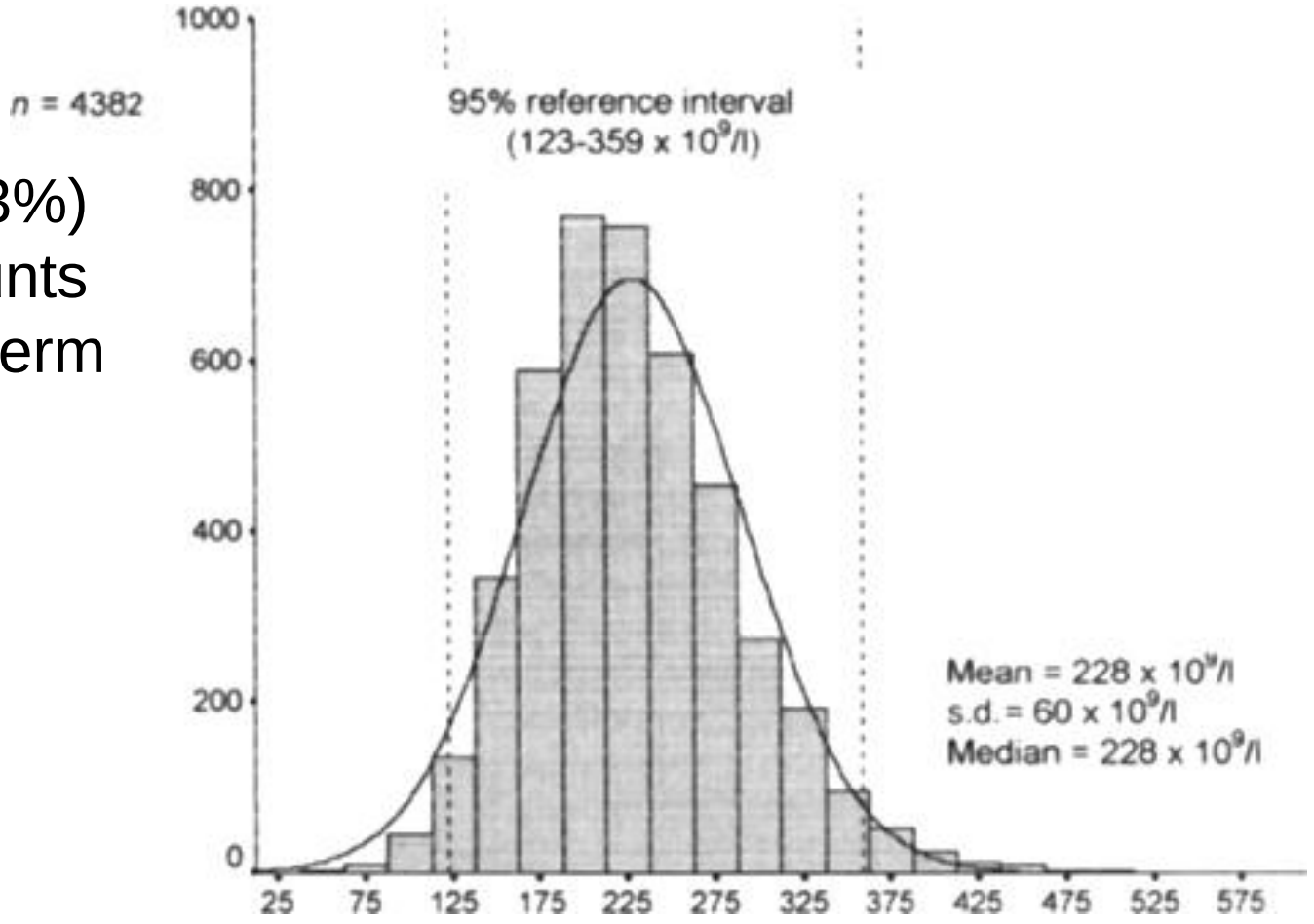
Thrombocytopenia in pregnancy: how common?

317 women (7.3%) had platelet counts <150 x 10^9/l at term



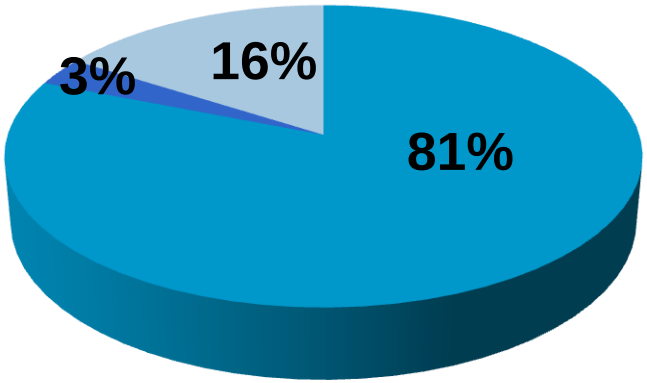
Saino et al, 2000;Acta Obstet Gynecol Scand: 79: 744-749

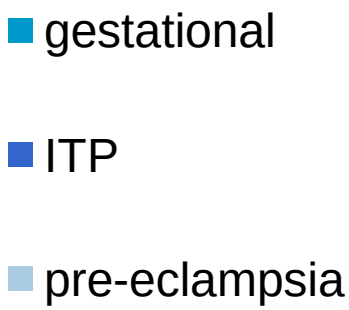
Thrombocytopenia in pregnancy: causes

- Physiological:
  - ‘gestational’/incidental thrombocytopenia
- Pre-eclampsia
- Immune thrombocytopenia (ITP)
- Microangiopathic syndromes
- All other causes: bone marrow failure, leukaemia, hypersplenism, DIC etc.

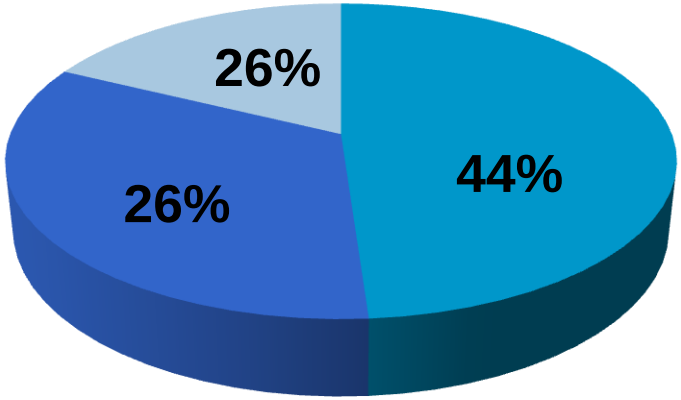
Thrombocytopenia in pregnancy: causes

Platelets < 150 x 10^9/l

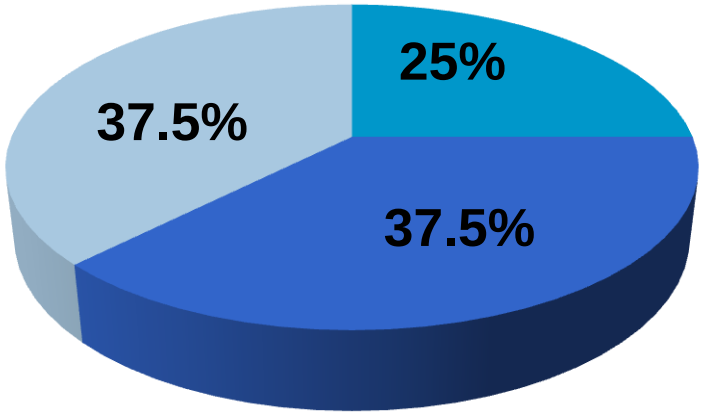




Platelets < 100 x 10^9/l



Platelets < 70 x 10^9/l



Saino et al, 2000;Acta Obstet Gynecol Scand: 79: 744-749

1. Gestational thrombocytopenia

- Physiological decrease in platelet count ~ 10%
- >50x10^9/l sufficient for delivery (>80 for epidural)
- Mechanism poorly defined
  - Dilution + increased consumption
- Baby not affected
- Platelet count rises D2 – 5 post delivery

2. Preeclampsia and thrombocytopenia

- 50% get thrombocytopenia
  - Proportionate to severity
- Probably due to increased activation and consumption
- Associated with coagulation activation
  - (incipient DIC – normal PT, APTT)
- Usually remits following delivery

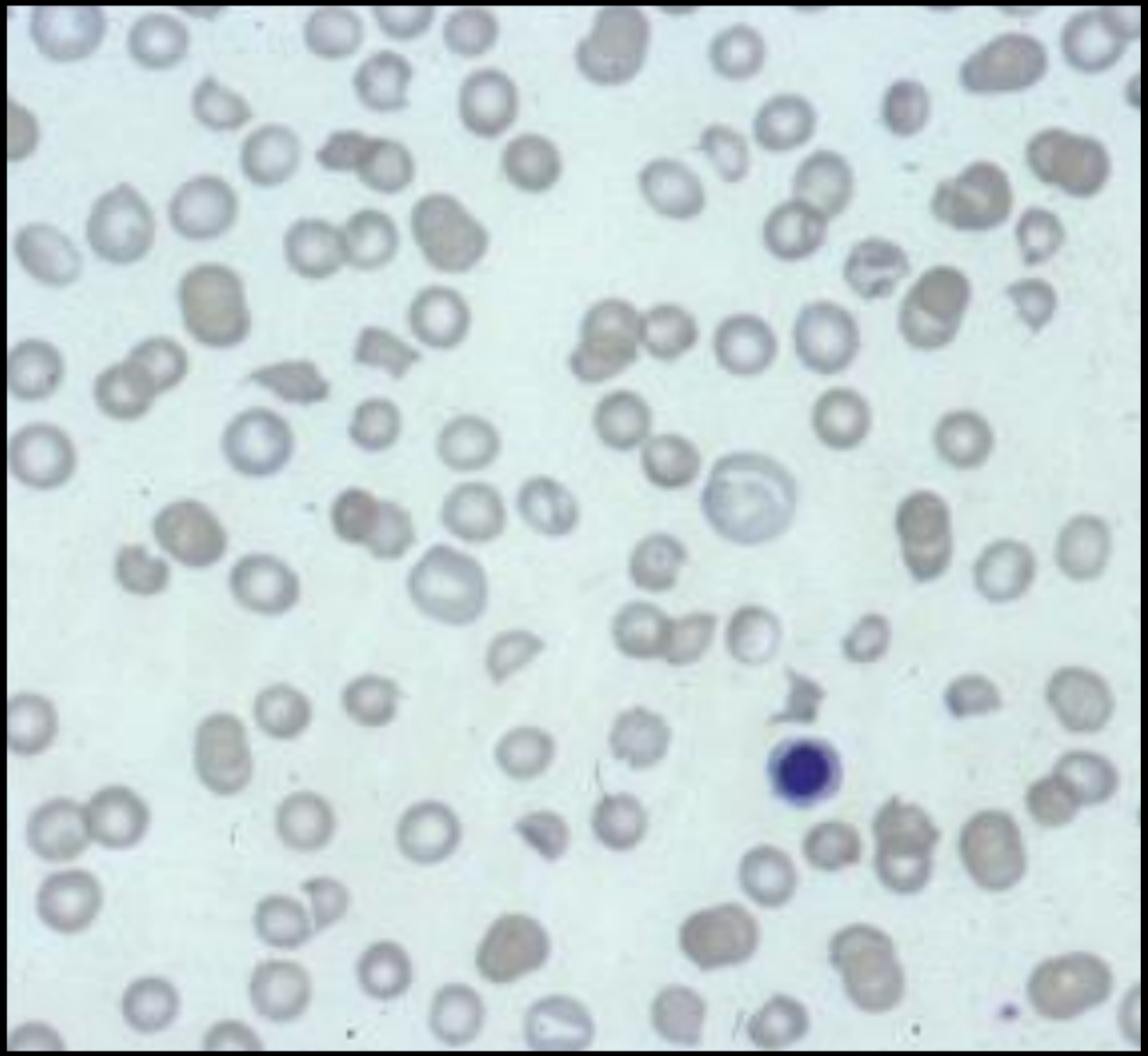
3. Immune thrombocytopenia (ITP)

- 5% of thrombocytopenia in pregnancy
  - TP may precede pregnancy
  - Early onset
- Treatment options (for bleeding or delivery)
  - IV immunoglobulin
  - Steroids etc.
  - (Anti-D where Rh D +ve)
- Baby may be affected
  - Unpredictable (platelets <20 in 5%)
  - Check cord blood and then daily
  - May fall for 5 days after delivery
  - Bleeding in 25% of severely affected (IVIG if low)
  - Usually normal delivery

4. Microangiopathic syndromes

- Microangiopathic haemolytic anaemia
  - Deposition of platelets in small blood vessels
  - Thrombocytopenia
  - Fragmentation and destruction of rbc within vasculature
  - Organ damage (kidney, CNS, placenta)

Microangiopathy – blood film



Fragments
Low platelets
polychromasia

4. Microangiopathic syndromes

- HELLP
  - Haemolysis, Elevated Liver enzymes, Low Platelets
  - Overlap with preeclampsia. May worsen for 48 hours after delivery.
- TTP & HUS
  - More common in pregnancy
  - Not helped by delivery
  - Earlier than HELLP, usually 2nd trimester

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Mortality in pregnancy

	1985 -87	1988- 90	1991- 93	1994- 96	1997- 99	2000 - 2003	2003 - 2005	2006 - 2008
VTE	32	33	35	48	35	30	41	18
Pre-eclampsia/ eclampsia	27	27	20	20	15	14	18	22
Ectopic	16	15	8	12	13	11	10	
Haemorrhage	10	22	15	12	7	17	14	9
Amniotic fluid embolism	9	11	10	17	8	5	17	13
Genital tract sepsis	9	17	15	16	18	13	18	26
All Direct deaths	139	145	128	134	106	106	132	107

Confidential Enquiry into Maternal and Child Health:

http://cemach.interface-test.com

Coagulation Changes in Pregnancy

Summary of major changes

Factor VIII and vWF	increase 3-5 fold
Fibrinogen	increases 2 fold
Factor VII	increases 0.5 fold
(Factor X)	
Protein S	falls to half basal
PAI-1	increase 5 fold
PAI-2 produced by placenta	

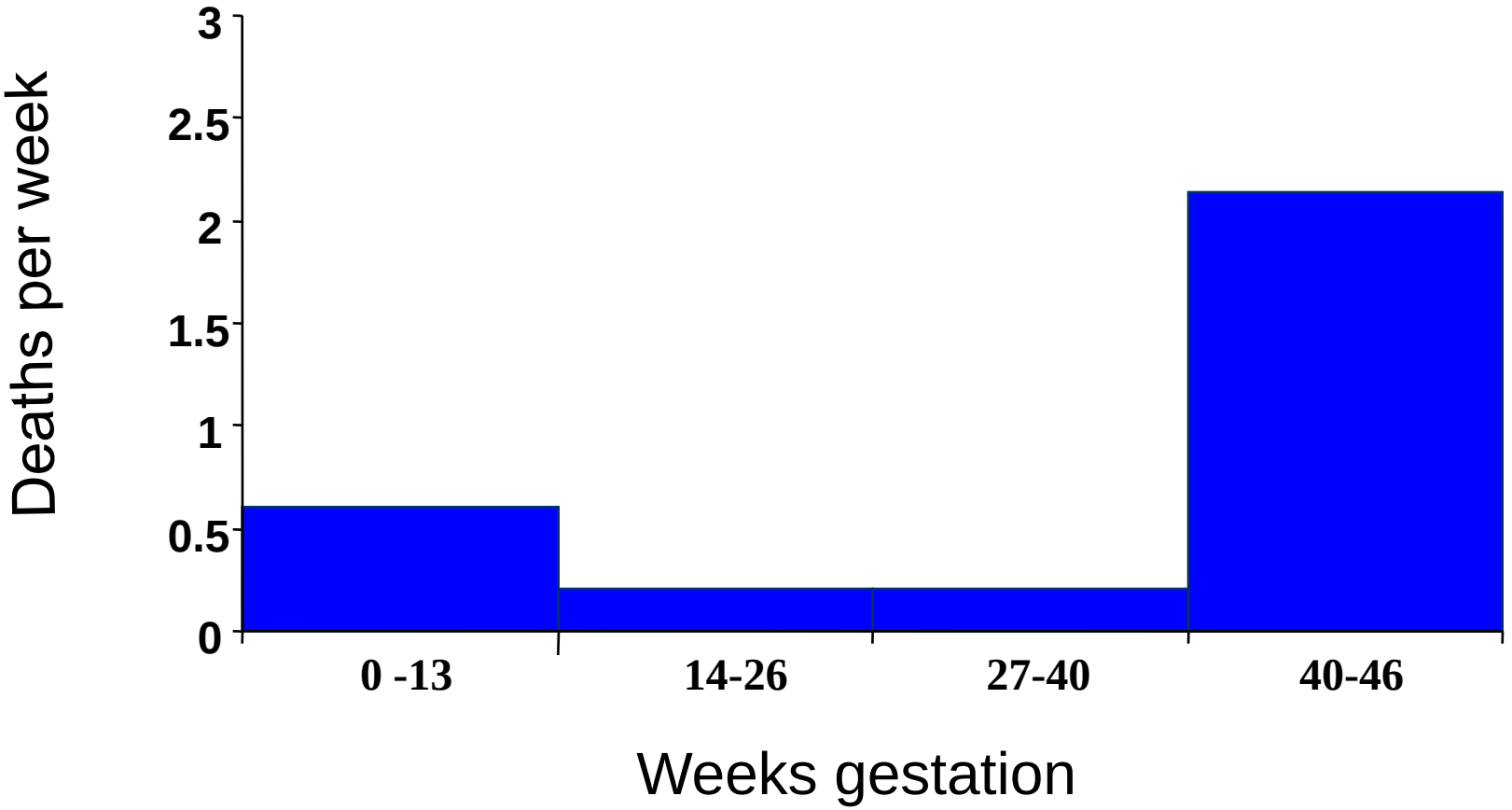
Coagulation Changes in Pregnancy

Net effects: a procoagulant state

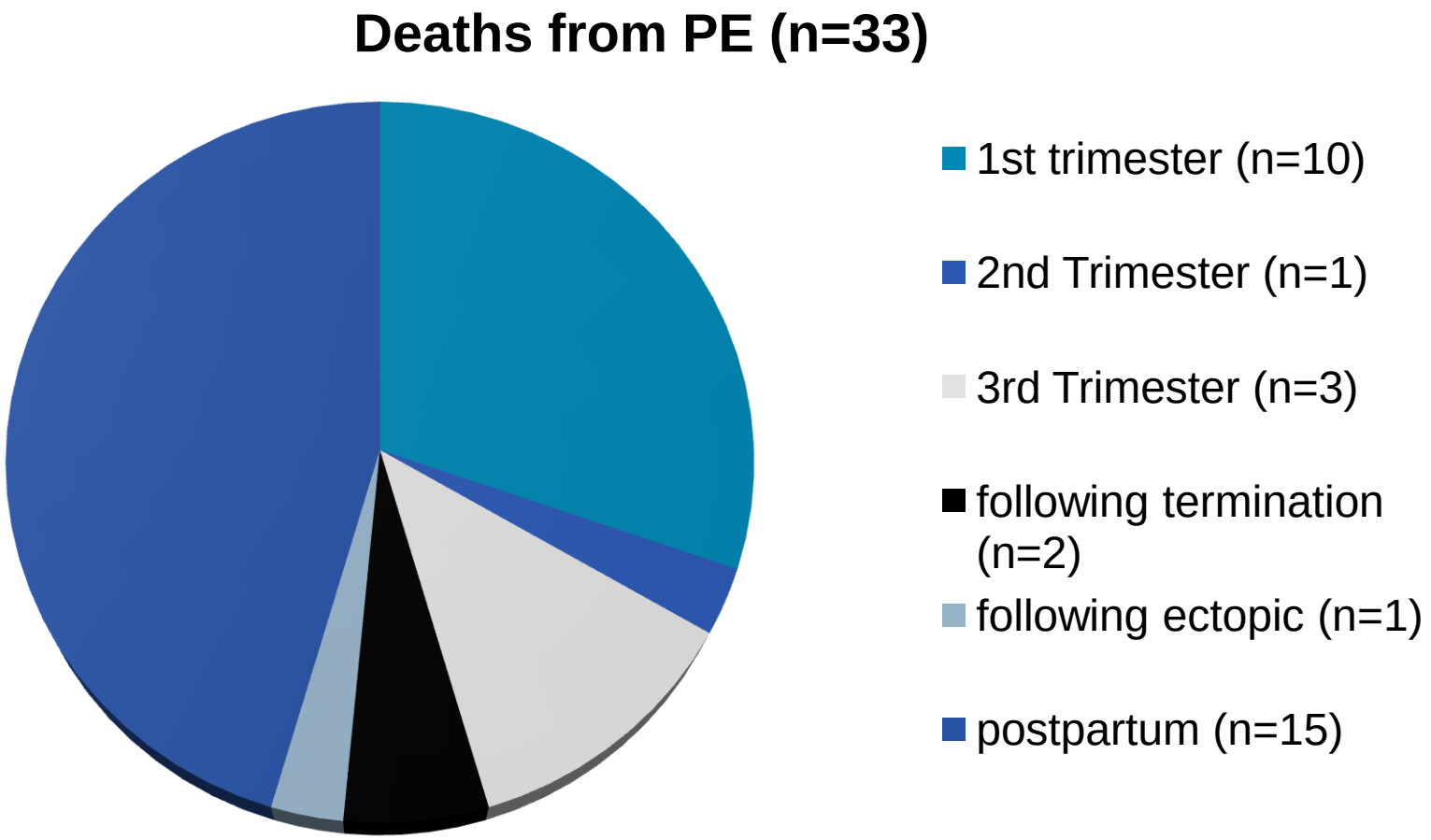
- Increased thrombin generation
- Increased fibrin cleavage
- Reduced fibrinolysis
- Interact with other maternal factors

Increased rate of thrombosis

Thromboembolic disease :
Deaths from Pulmonary Embolism in Pregnancy



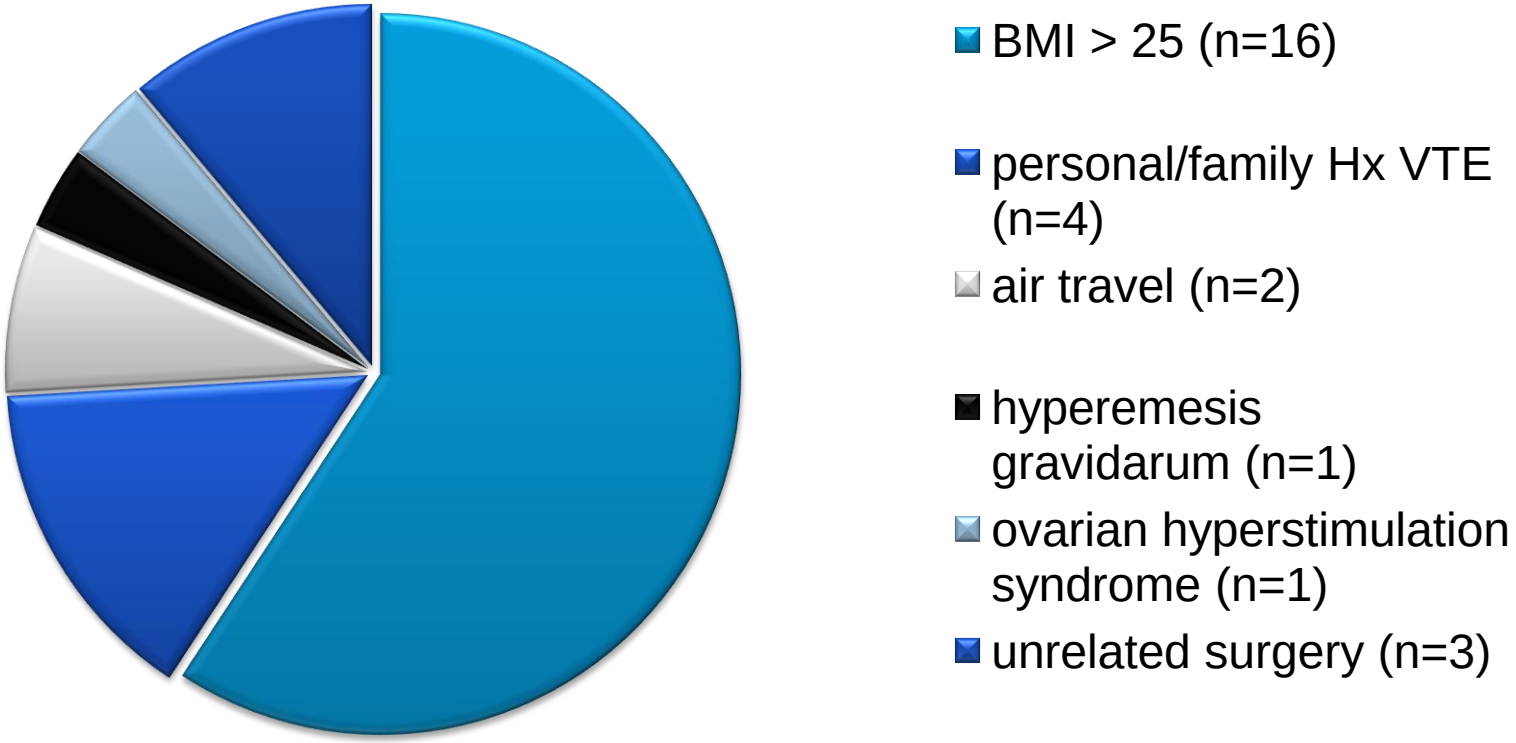
Confidential Report on Maternal Deaths 2003 -2005



CEMACH 2007

Confidential Report on Maternal Deaths 2003 - 2005

Risk factors for VTE identified in women who died of PE (n=26)



CEMACH 2007

Thromboembolic disease: Incidence of thrombosis in pregnancy

- 1 per 1000 <35 years
- 2 per 1000 >35 years
- Relative risk approx. x10
- 1/1000 for pregnancy and 0.5 in puerperium
- One third are post partum (only 6 weeks)

- Doppler and VQ are safe to perform in pregnancy
- D-dimer often elevated in pregnancy
  - Not useful for exclusion of thrombosis

Thromboembolic disease: Factors increasing risk of thrombosis in pregnancy

All

- Changes in blood coagulation
- Reduced venous return
- Vessel wall

Variable

Hyperemesis/dehydration

- Bed rest
- Obesity
  - BMI>29 3x risk of PE
- Pre-eclampsia
- Operative delivery
- Previous thrombosis/thrombophilia
- Age
- Parity
- Multiple pregnancy
- Other medical problems:
  - HbSS, nephrotic syndrome
- IVF: ovarian hyperstimulation

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Thromboembolic disease: Factors increasing risk of thrombosis in pregnancy

All

- Changes in blood coagulation
- Reduced venous return
  - ~85% Left DVT
- Vessel wall

Variable

Hyperemesis/dehydration

- Bed rest
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  - BMI>29 3x risk of PE
- Pre-eclampsia
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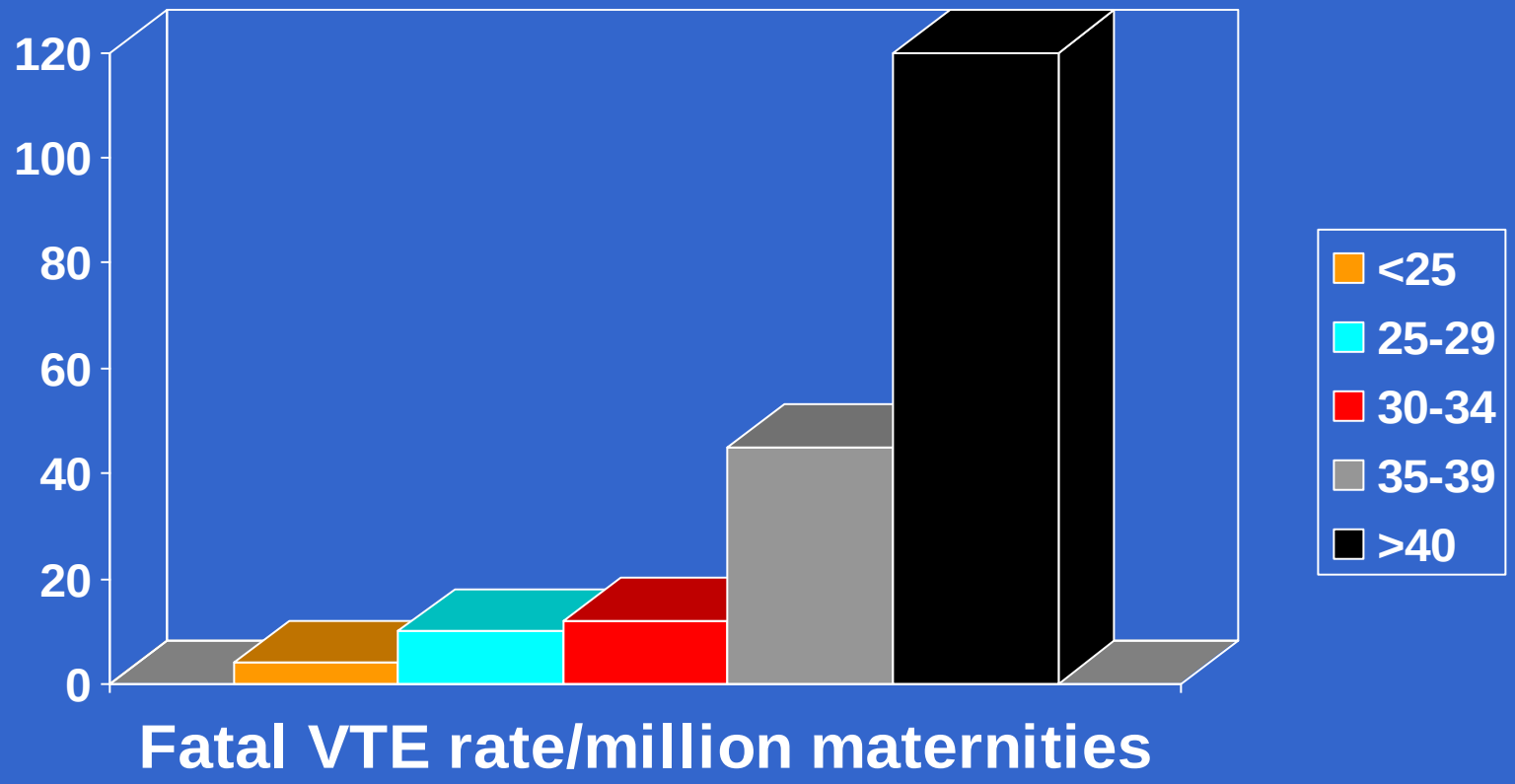
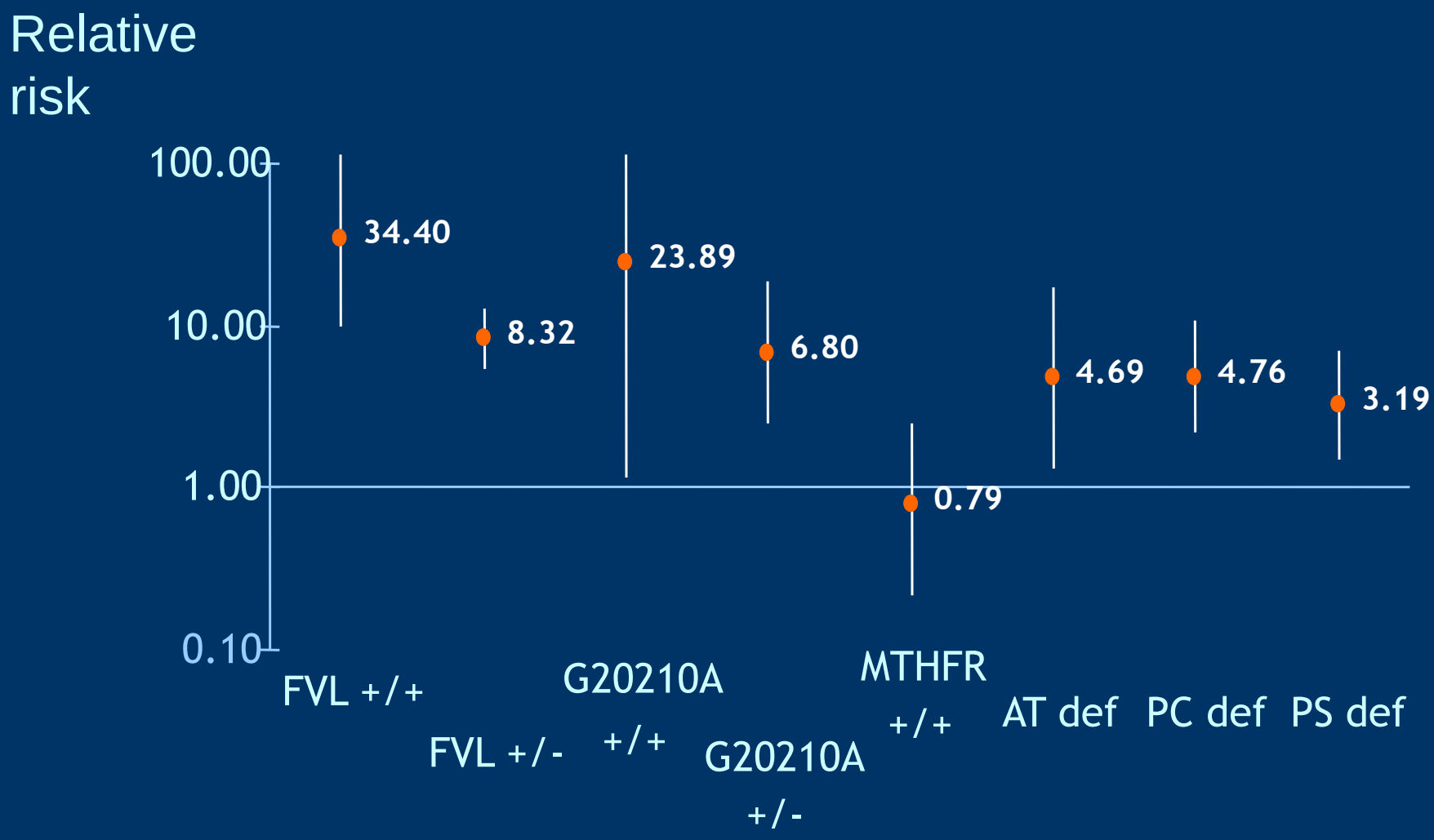
Age and risk of fatal VTE in pregnancy
(from UK CEMD 1985-90)



VTE and inherited thrombophilia



Robertson et al, BJH 2005, 132:171-196

Confidential Report on Maternal Deaths:

Reduction in VTE mortality rates 2006 – 2008

Improved assessment of risk

Public health education: identify women at risk because of their weight, family history or past history to seek advice before becoming pregnant. RCOG guidelines 2004

Increased recognition of symptoms in early pregnancy - chest pain / SOB / leg pain

Diagnosis - Increased awareness that diagnostic tests (VQ / CXR / Venogram/ CTPA) are safe

Treatment

- Wider use of thromboprophylaxis
- Therapy should be given pending the results of further testing

RCOG Green-top Guidelines 2009

Antenatal Assessment & Management

(To be assessed at booking and repeated if admitted)

- Single previous VTE +
  - Thrombophilia, or FH
  - Unprovoked/oestrogen related
- Previous recurrent VTE (>1)

→ **High Risk**

Requires antenatal prophylaxis with LMWH

Refer to Trust nominated thrombosis in pregnancy expert / team.

- Single previous provoked VTE without FH or thrombophilia
- Thrombophilia + no VTE
- MEDICAL CO-MORBIDITIES e.g. Heart or Lung disease; SLE; Cancer; Inflammatory conditions; Nephrotic syndrome; Sickle Cell Disease; IVDU
- Surgical Procedure e.g. appedicectomy

→ **Intermediate Risk**

Consider antenatal prophylaxis with LMWH

Seek Trust nominated thrombosis in pregnancy expert / team advice.

- Age > 35 yrs
- Obesity (BMI>30kg/m^2)
- Parity ≥ 3
- Smoker
- Gross varicose veins
- Current systemic infection
- Immobility, e.g. paraplegia, SPD, long-haul travel
- Pre-eclampsia
- Dehydration/hyperemesis/OHSS
- Multiple pregnancy or ART

→ 3 or more risk factors

2 or more if admitted

→ <3 risk factors

→ **Lower Risk**

Mobilisation and avoidance of dehydration.

Postnatal Assessment & Management

(to be assessed on Delivery Suite)

- Any previous VTE
- Asymptomatic Thrombophilia
- Anyone requiring antenatal LMWH

→ **High Risk**

At least 6 weeks postnatal prophylactic LMWH

- Caesarean Section in Labour
- APL + no previous VTE
- BMI > 40 kg/m^2
- Prolonged Hospital Admission
- MEDICAL CO-MORBIDITIES e.g. Heart or Lung disease; SLE; Cancer; Inflammatory conditions; Nephrotic syndrome; Sickle Cell Disease; IVDU

→ **Intermediate Risk**

At least 7 days postnatal prophylactic LMWH

NB If persisting or > 3 risk factors consider extending thromboprophylaxis with LMWH

- Age > 35 yrs
- Obesity (BMI>30kg/m^2)
- Parity ≥ 3
- Smoker
- Elective Caesarean Section
- Any surgical procedure in the puerperium
- Gross varicose veins
- Current systemic infection
- Immobility, e.g. paraplegia, SPD, long-haul travel
- Pre-eclampsia
- mid-cavity or rotational forceps
- Prolonged labour (>24 hrs)
- PPH > 1litre or Blood Transfusion

→ 2 or more risk factors

→ < 2 risk factors

→ **Lower Risk**

Early mobilisation and avoidance of dehydration.

Obstetric Thromboprophylaxis Risk Assessment & Management

Thromboembolic disease: prevention in pregnancy

- Women with risk factors should receive prophylactic heparin +TED stockings
  - Either throughout pregnancy
  - Or in peri-post- partum period
  - Highest risk get adjusted dose LMWH heparin
- Mobilise early
- Maintain hydration

Thromboembolic disease: treatment in pregnancy

- Management
  - LMWH as for non-pregnant
    - Does not cross placenta
    - RCOG recommend once or twice daily
  - Do not convert to warfarin (crosses placenta)
  - After 1st trimester monitor anti Xa
    - 4 hour post 0.5-1.0u/ml
- Stop for labour or planned delivery, esp. for epidural
  - Epidural: wait 24 hours after treatment dose, 12 hours after prophylactic dose

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  - Sickle cell disease and pregnancy
- Immune disorders

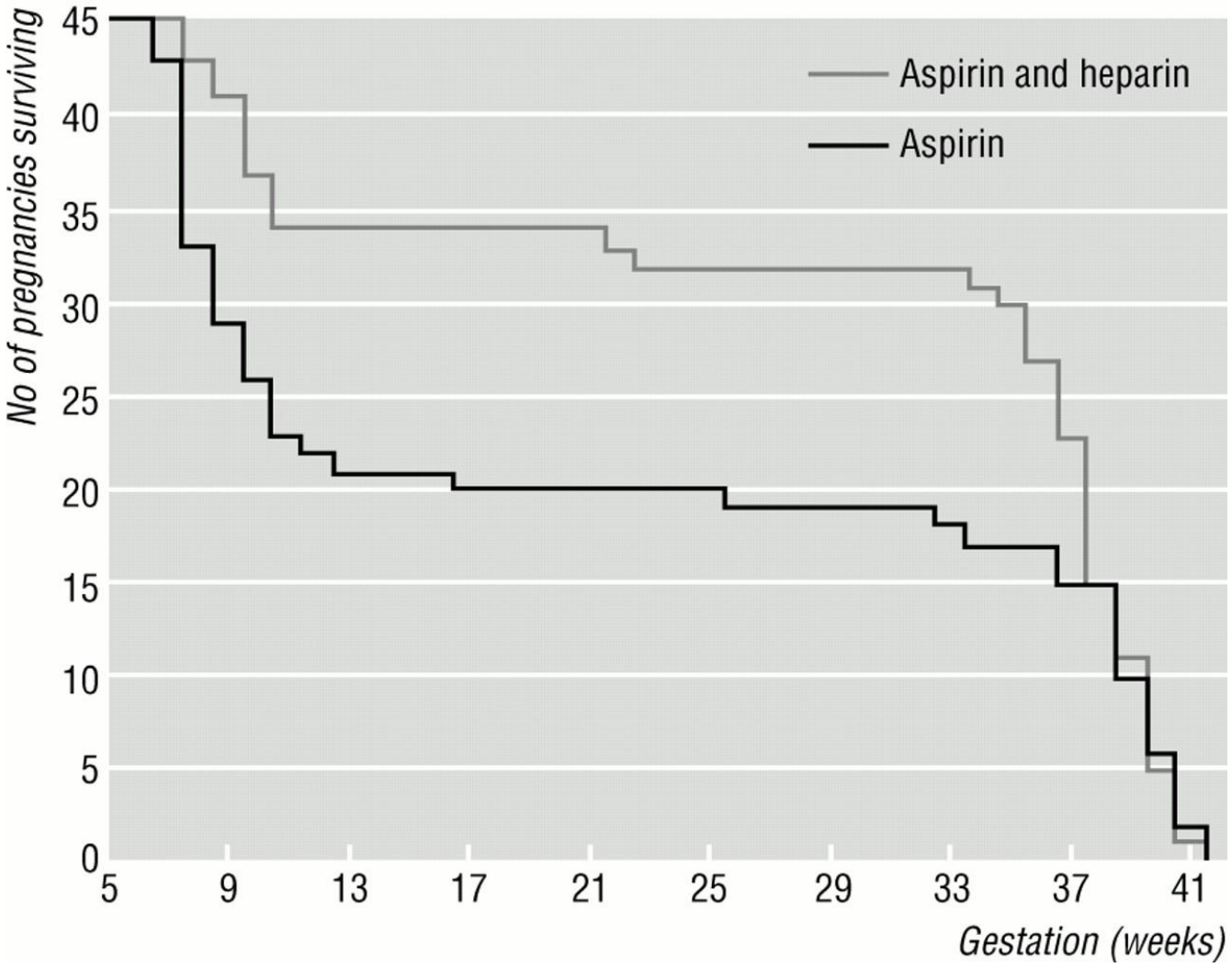
Thrombophilia and complications of pregnancy

- Hypothesis:
  - An increased tendency to thrombosis is associated with impaired placental circulation
- Resulting in
  - Fetal growth restriction (IUGR)
  - Recurrent miscarriage
  - Late fetal loss
  - Abruptio placentae
  - Severe PET

Thrombophilias that may be associated with pregnancy complications

- Antiphospholipid Syndrome (APLS): Recurrent miscarriage + persistent Lupus anticoagulant (LA)/ anticardiolipin antibodies (ACL)
- AT, PC,PS deficiency
- Factor V Leiden
- PTG20210A (high prothrombin)
- Hyperhomocysteinemia (HHC)

Women with recurrent miscarriage and antiphospholipid antibodies



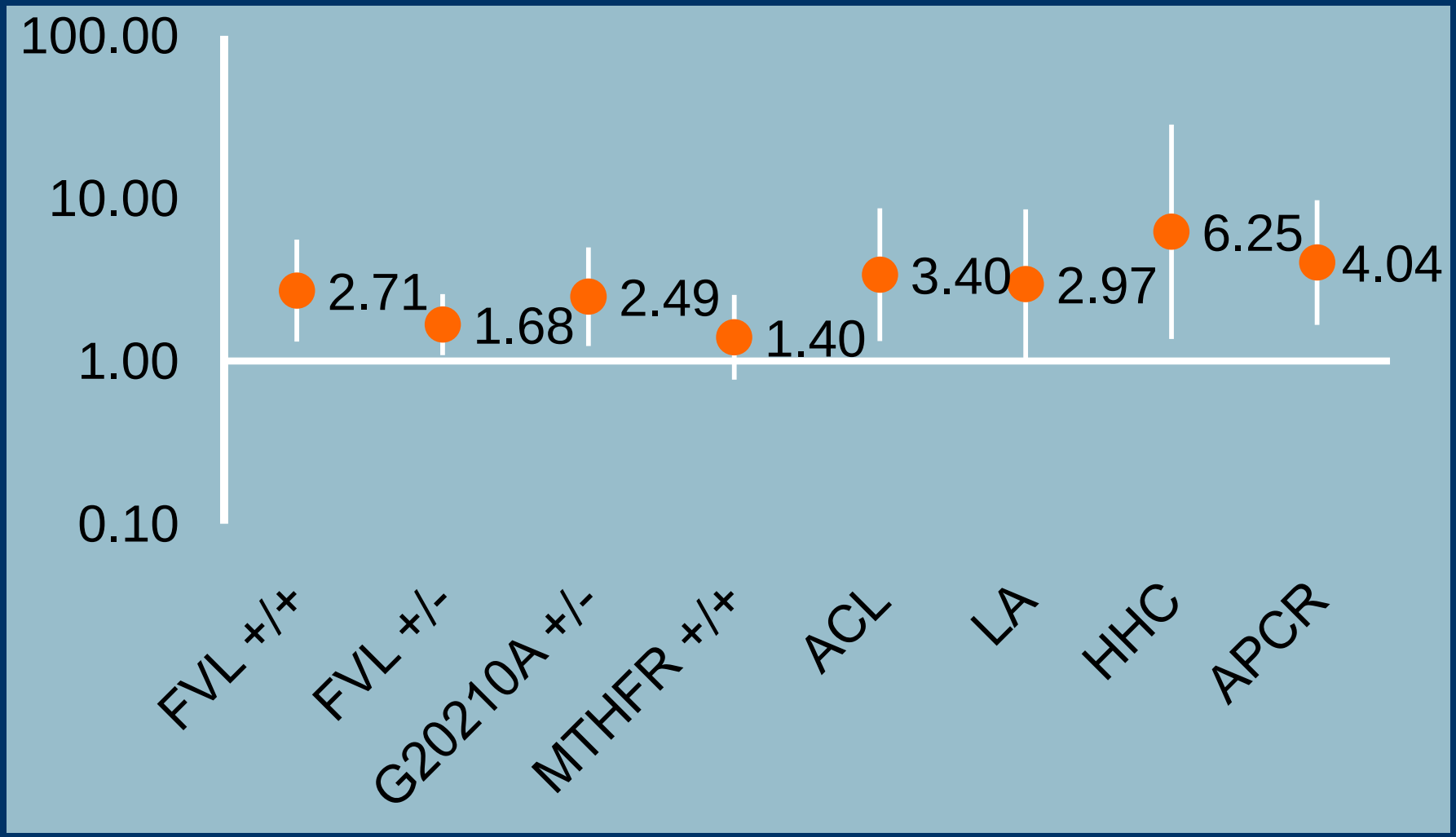
Live births

71%
Vs
42%

Rai 1997

Early pregnancy loss

(spontaneous loss in 1st or 2nd trimester)



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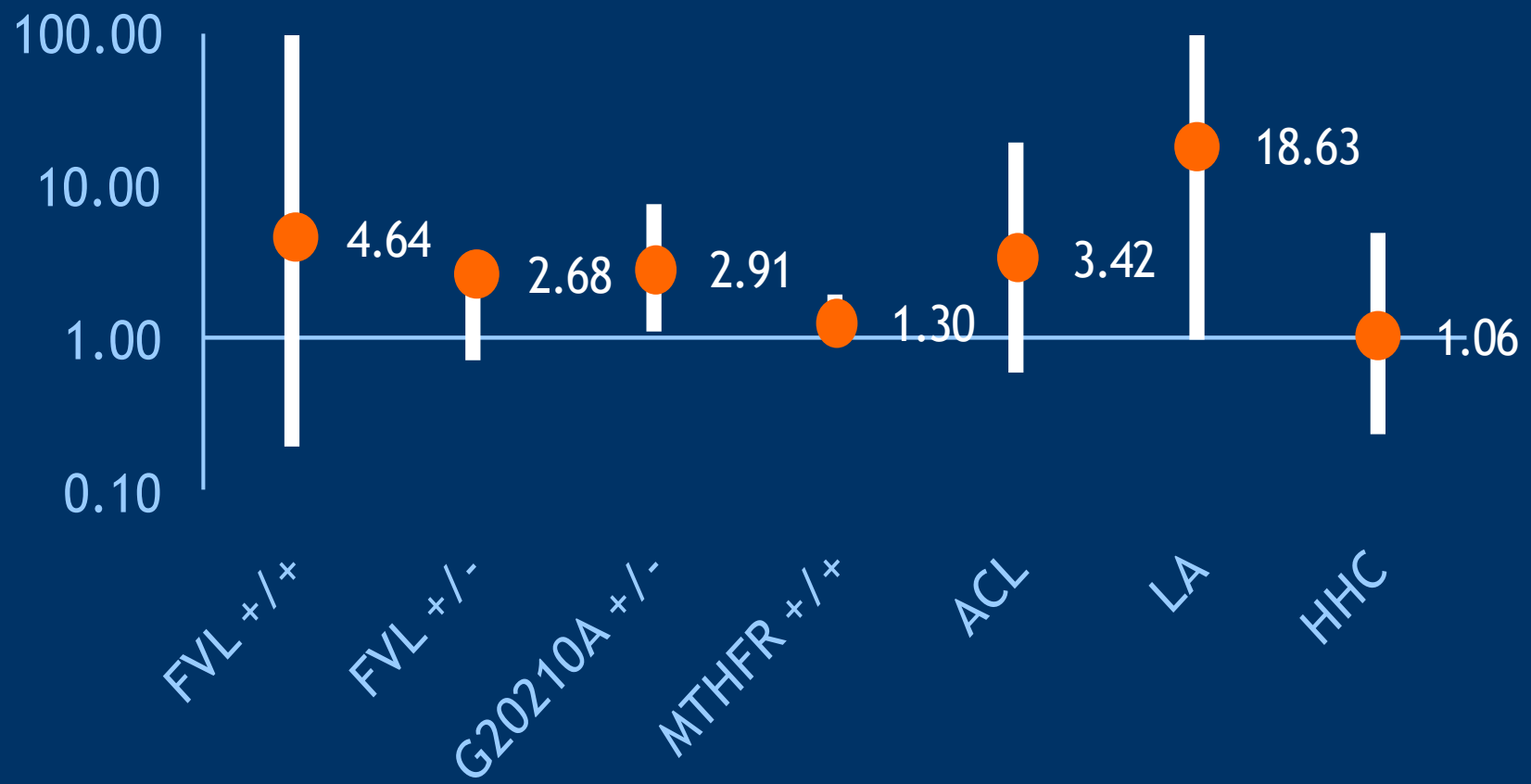
Thrombophilia and IUGR



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Placental abruption

Robertson 2006

Pregnancy complications and coagulation

- Following success with APLS, the reported association with heritable thrombophilias led to pragmatic use of Aspirin and Heparin
- However, recent RCTs* fail to demonstrate improvement in pregnancy outcome in unselected women with idiopathic recurrent pregnancy loss with aspirin/heparin
- Large ongoing RCT aspirin/heparin in other pregnancy complications

**Clark et al, Blood 2010; Kaandorp et al, NEJM 2010; Visser et al Thromb Haemost 2011; Laskin et al, J Rheum 2009*

Recurrent pregnancy loss, thrombophilia testing and heparin/aspirin 2011*

- Consider limitations of available data and potential benefits and harms of any intervention
- BCSH recommend against antithrombotic therapy in pregnant women with history of pregnancy loss based on results of thrombophilia testing (2010)
- ACCP no longer recommend (2008):
  - screening for hereditary thrombophilia in women with rec. pregnancy loss
  - use of antithrombotics in women with inherited thrombophilia and rec. loss
- Heparin shown to have potentially beneficial effects on trophoblast that may facilitate implantation
  - Future research examining time of implantation .

* Except APLS

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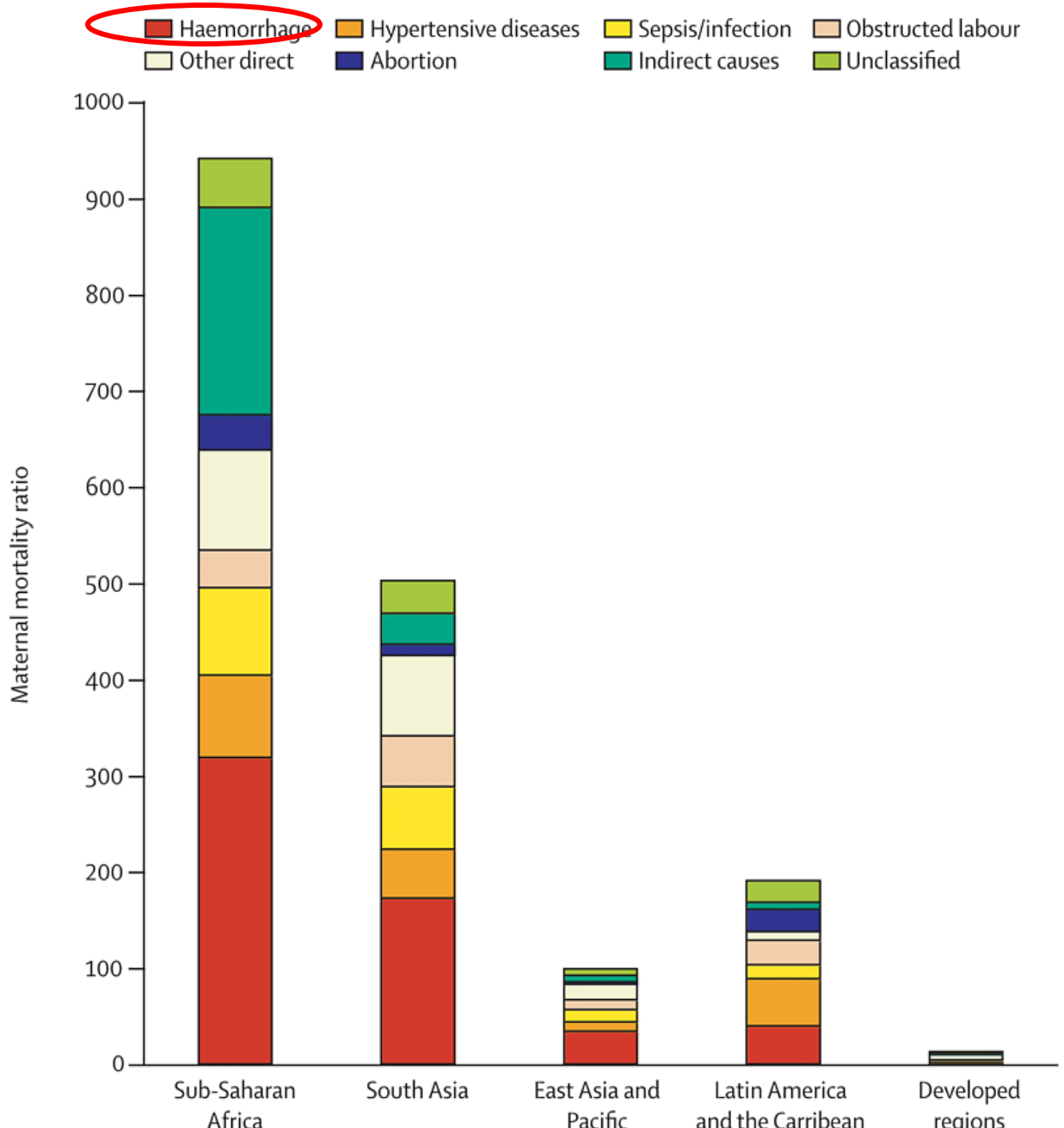
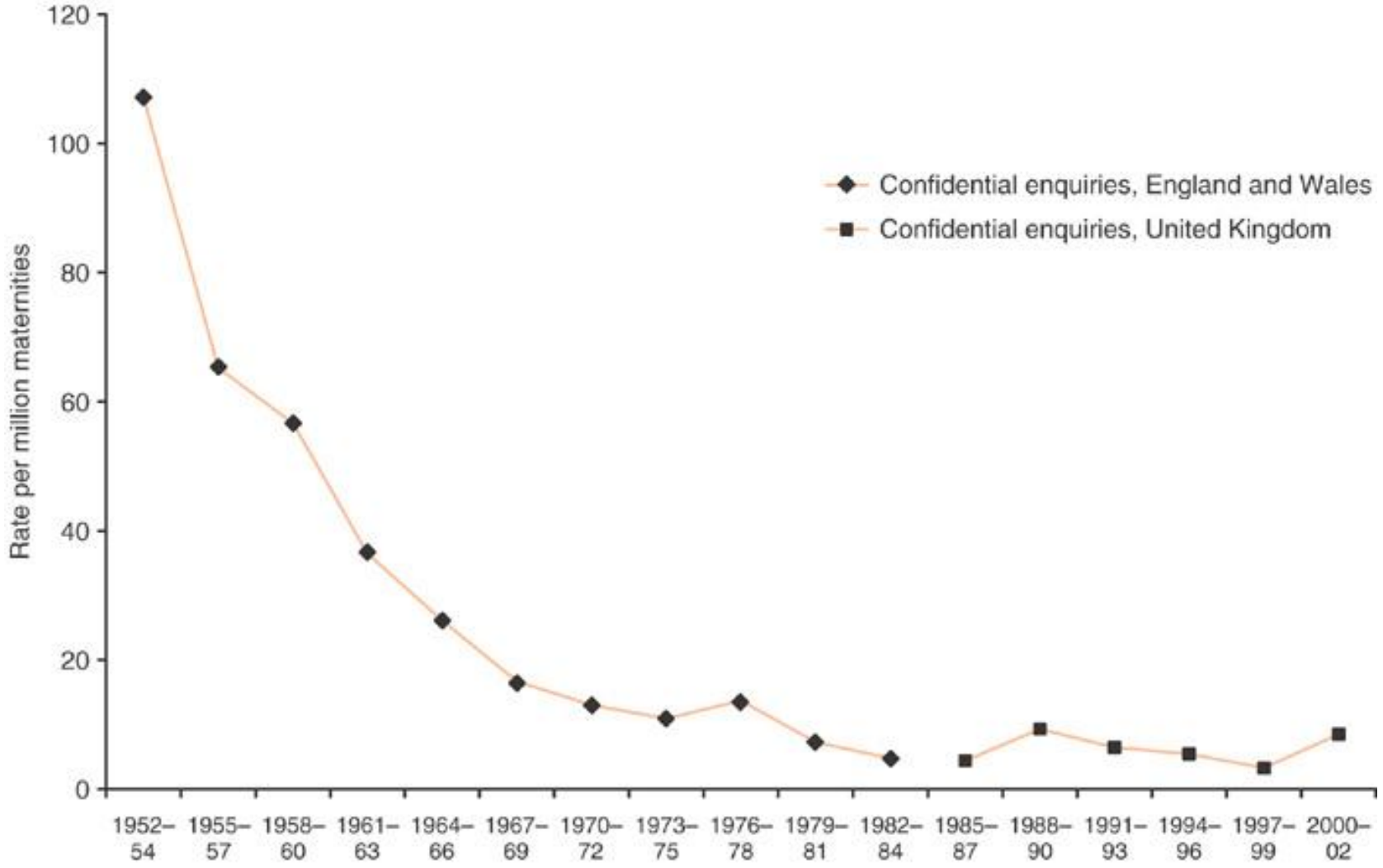
Maternal mortality ratios 2000



Ronsmans, 2006

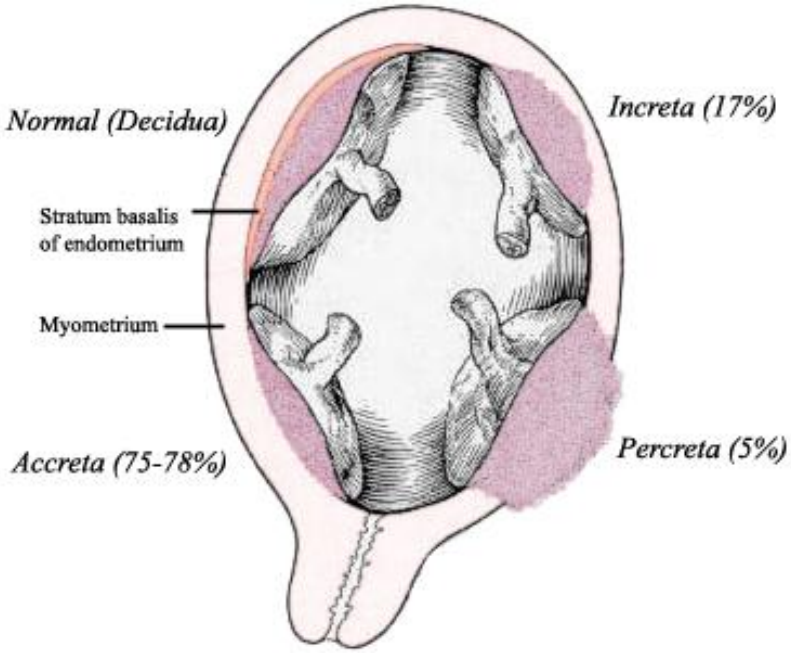
Maternal mortality rates from haemorrhage



Fatal bleeding in pregnancy

- CEMACH 2006 -2008
  - 9 deaths from haemorrhage
    - 2 placenta praevia
    - Placenta accreta

  principal reason for hysterecetomy



- Use of Major Obstetric Haemorrhage protocols
- Determine placental site if previous C-Section

Non-fatal bleeding in pregnancy

- ‘Normal’ average blood loss
  - Vaginal 300-500ml
  - C-Section 900-1100
- Post Partum Haemorrhage (PPH)
  - 40% after vaginal delivery (>500ml)
  - 30% after C-Section (>1100ml)
- Requiring transfusion post partum
  - 1% after vaginal delivery
  - 1-7% after C-Section

Postpartum Haemorrhage: mechanisms

- major factors are
  - uterine atony
  - trauma
- haematological factors minor except
  - dilutional coagulopathy after resuscitation
  - DIC in abruption, amniotic fluid embolism etc.

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Pregnancy and Disseminated Intravascular Coagulation (DIC)

- Coagulation changes in prenancy predispose to DIC.
- Decompensation precipitated by:
  - Amniotic fluid embolism
  - Abruptio placentae
  - Retained dead fetus
  - Preeclampsia (severe)
  - Sepsis

Amniotic fluid embolism

- ‘the most catastrophic event in modern obstetrics’
- 1 in 20000-30000 births
- Sudden onset shivers, vomiting, shock. DIC
- 86% mortality
  - 13 deaths in last triennium
- Presumed due to Tissue Factor in amniotic fluid
- Almost all >25 years
- Usually third trimester
- No association with parity

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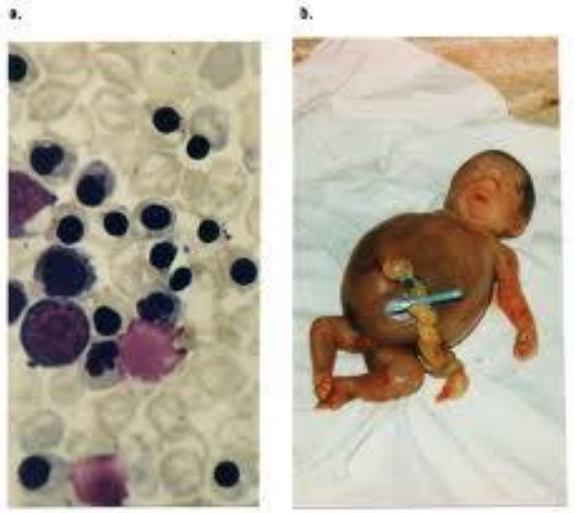
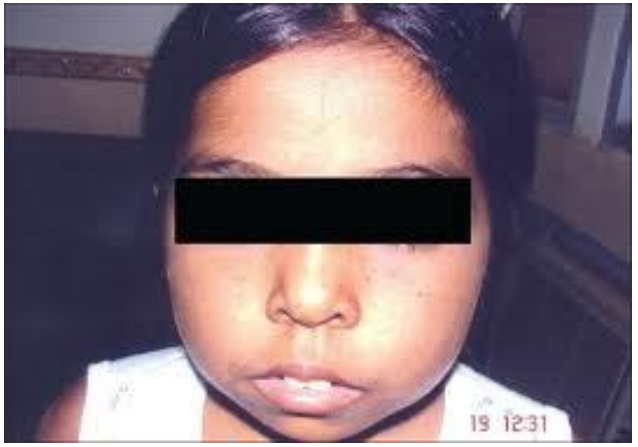
Haemoglobinopathy screening Aims:



To avoid birth of children with:

- α° thalassaemia (Hb Bart's, γ^4)
  - Death in utero, hydrops fetalis
- β° thalassemia
  - Transfusion dependent
- HbSS (sickle cell disease)
  - Life expectancy 43 yrs
- Other compound HbS syndromes
  - Symptomatic, stroke etc.
- Some compound thalassaemias
  - Transfusion dependent, iron overload

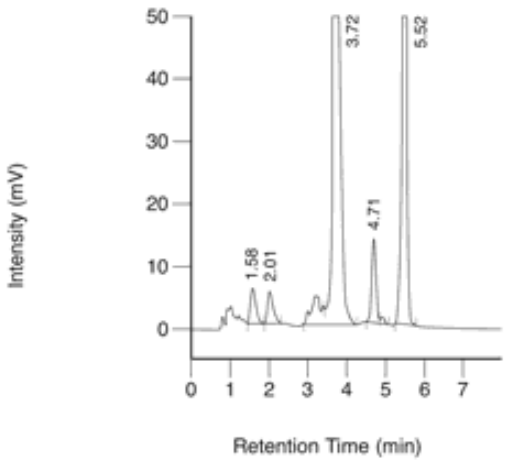


Haemoglobinopathy screening Practice:

- All pregnant women in England offered screening for Thalassaemia based on FBC indices
- Screening for sickle cell & other haemoglobinopathies:
  - Low prevalence <15% at risk: ethnic minorities
  - High prevalence >15% at risk: universal screening
- West London: All women have FBC and HPLC analysis at booking
- www.sickleandthal.org.uk

Haemoglobinopathy detection

- HPLC
  - Identifies Hb variants eg: S, C, E
  - Quantifies Hb A_2 (>3.5% → beta thal)
- Red cell indices
  - MCH <27 possible thalassaemia trait
  - MCH <25 possible alpha thal trait.
    - Alpha thal requires DNA analysis



(only important to detect alpha zero trait – likelihood is assessed on ethnic origin. Far east, SE Asia, Greece and Turkey)

Haemoglobinopathy- counselling

- Important disorders are all recessive
- Therefore if mother is heterozygous partner should be tested.
- Combinations as important as homozygous states
- Options
  - Proceed
  - Prenatal diagnosis@
    - CVS sampling (10-12 weeks)
    - Amniocentesis, fetal blood sampling
  - Ultrasound screening for hydrops

Effect of thalassaemia screening in N Cyprus

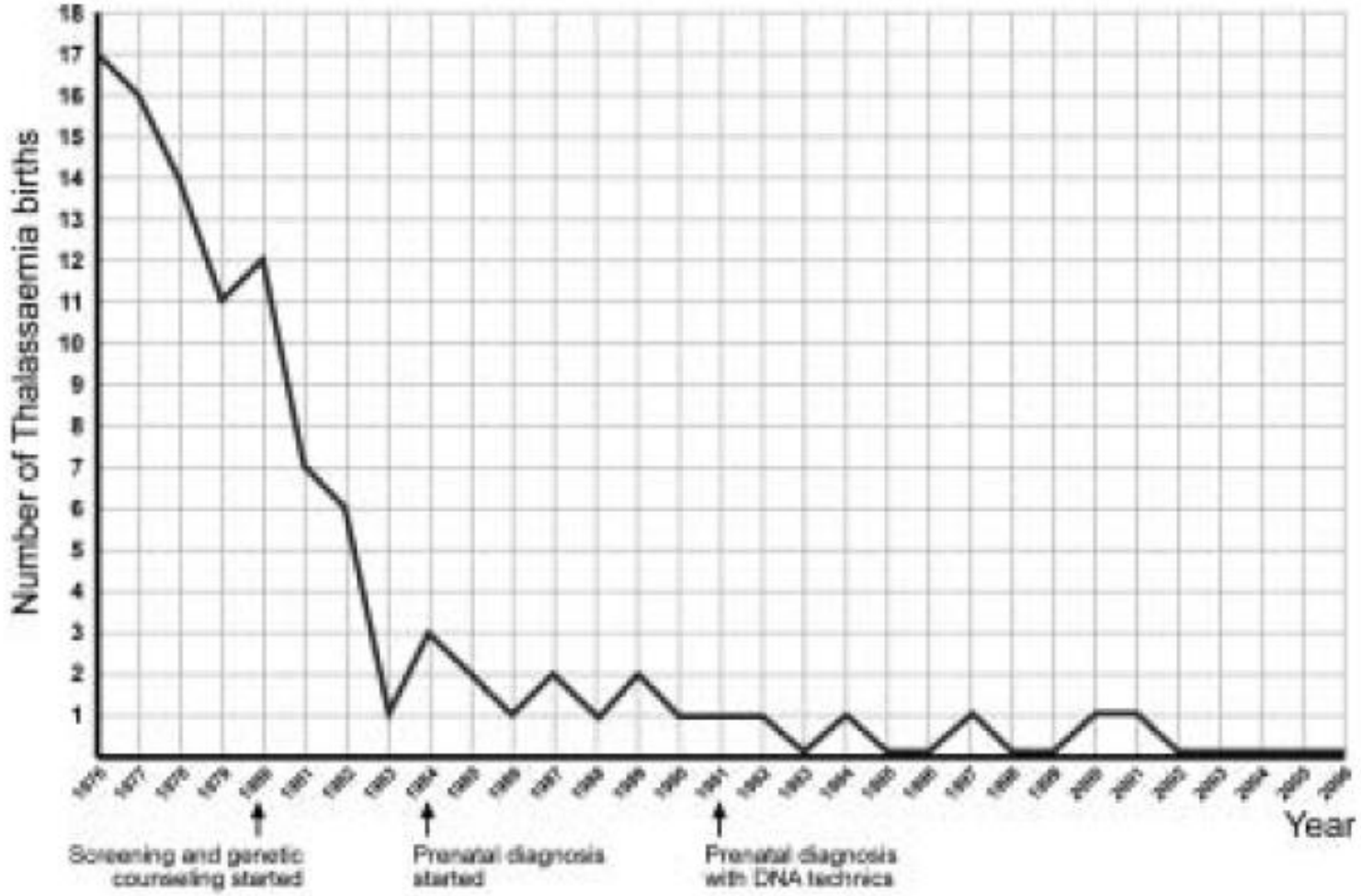


FIGURE 1 Graph showing the decrease in the number of babies born with homozygous β-thal in North Cyprus (1976–2006).

Sickle cell anaemia in pregnancy

- Painful crises become more frequent
- Anaemia exaggerated
- Transfusion/exchange transfusion often required

Sickle cell anaemia in pregnancy

	% of SS pregnancies	*Relative risk and 95% confidence interval**
Antepartum hospital admission	62	6.8 (3.8-11.9)
Preterm labor or preterm premature rupture of membranes	13	2.8 (1.1-7.6)
Prematurity	45	4.1 (2.4-7.2)
Low birth weight	46	2.7 (1.7-4.3)
IUGR	45	4.9 (2.7-8.9)
Pyelonephritis	7	3.1 (0.8-12.8)
Preeclampsia	10	1.9 (0.7-4.2)
Postpartum infection	22	9.4 (2.8-31.4)
Intrauterine fetal death	4	5.7 (0.6-53.0)
Perinatal mortality	11	3.0 (1.0-8.9)

*Referent group, AA pregnancies.

Other important disorders in pregnancy

- Haemolytic disease of the newborn (HDN)
- Neonatal alloimmune thrombocytopenia (NAITP)

Maternal immune responses against fetal antigens requiring monitoring and intervention during pregnancy.