Abnormal pregnancy

- **Definition**
- Incidence
- Risk factors
- Pathophysiology
- Presentation, signs and symptoms
- Diagnosis
- Special investigations
- Treatment
- Screening and prevention

- Points of highlighted subtitles

International classifications of diseases ICD-11 group #18
Pregnancy, childbirth or the puerperium

- Abortive outcome of pregnancy
- Oedema, proteinuria, or hypertensive disorders in pregnancy, childbirth, or the puerperium
- Obstetric haemorrhage
- Certain specified maternal disorders predominantly related to pregnancy (hyperemesis, venous complications, infections, diabetes, malnutrition, findings of antenatal screening, complications of anaesthesia)
- Maternal care related to the fetus, amniotic cavity or possible delivery problems (multiple gestation, malpresentation, dysproportion, polyhydramnion, premature rupture of membranes, placental disorders, prolonged pregnancy)

Selected subjects to be presented should always be based on their importance (that is morbidity and mortality)

- Gestational diabetes
- Preeclampsia
- Haemorrhagic complications

Gestational diabetes

- **Definition of gestational diabetes**
- **Incidence**
- **Risk factors**
- **Pathophysiology**
- **Presentation, signs and symptoms**
- **Fetal growth**
- **Diagnosis**
- **Special investigations**
- **Treatment**
- **Screening and prevention**

- Any degree of glucose intolerance with onset of first recognition during pregnancy
- Fasting serum glucose >7,1 mmol/L
- Random plasma glucose >11,1 mmol/L
- The definition applies whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy.

Gestational diabetes

- Definition of gestational diabetes
- Incidence
- Risk factors
- Pathophysiology
- Placentation
- Presentation, signs and symptoms
- Fetal growth
- Diagnosis
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- 7% of all pregnancies
- Prevalence varies between 1-14%
- Common complications

Fetal macrosomia

Urinary tract infection

Preterm delivery

Preeclampsia

Delayed lung maturation, IRDS

Neonatal jaundice, polycytaemia, hypocalcaemia, seizures

Perinatal death

Long-term CVD consequences in mother and offspring

Gestational diabetes

- Definition of gestational diabetes
- Incidence
- Risk factors
- Pathophysiology
- Presentation, signs and symptoms
- Fetal growth
- Diagnosis
- Special investigations
- Treatment
- Screening and prevention

- Multiparity
- Advanced age
- Family history of diabetes
- Previous GDM
- High prepregnancy BMI
- Autoimmune diseases
- Smoking
- American African/Hispanic/Asian ethnicity
- Sedentary lifestyle

Gestational diabetes

- Definition of gestational diabetes
- Incidence
- Risk factors
- **Pathophysiology**
- Presentation, signs and symptoms
- Fetal growth
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- β-cell dysfunction
- Insulin independent placental glucose-transport
- Suppressed insulin-receptor signalling
- ↑ Leptin level
- ↓ Adiponectin level

Plows et al. Int. J. Mol. Sci. **2018**, 19, 3342; doi:10.3390/ijms19113342

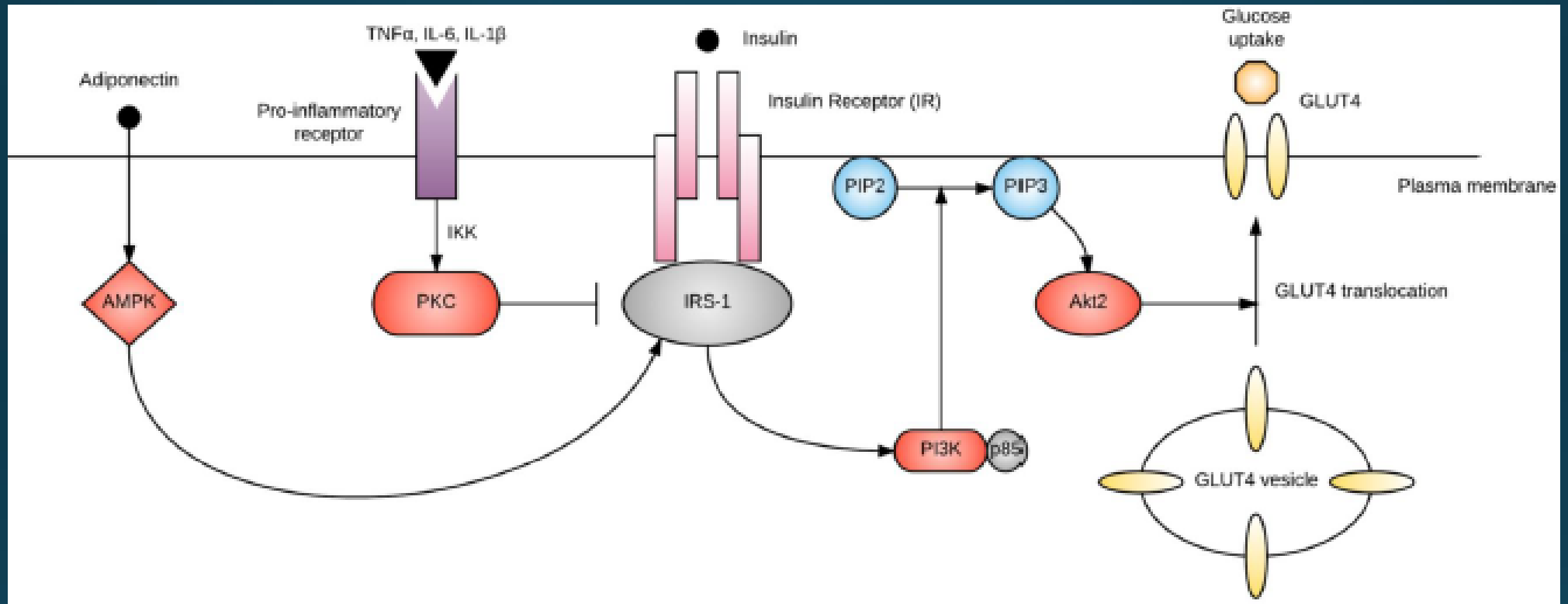

Figure 1. Simplified diagram of insulin signaling. Binding of insulin to the insulin receptor (IR) activates IRS-1. Adiponectin promotes IRS-1 activation through AMP-activated protein kinase (AMPK), while pro-inflammatory cytokines activate protein kinase C (PKC) via IκB kinase (IKK), which inhibits IRS-1. IRS-1 activates phosphatidylinositol-3-kinase (PI3K), which phosphorylates phosphatidylinositol-4, 5-bisphosphate (PIP2) to phosphatidylinositol-3, 4, 5-phosphate (PIP3). PIP3 activates Akt2, which promotes GLUT4 translocation and glucose uptake into the cell.

Plows et al. Int. J. Mol. Sci. **2018**, 19, 3342; doi:10.3390/ijms19113342

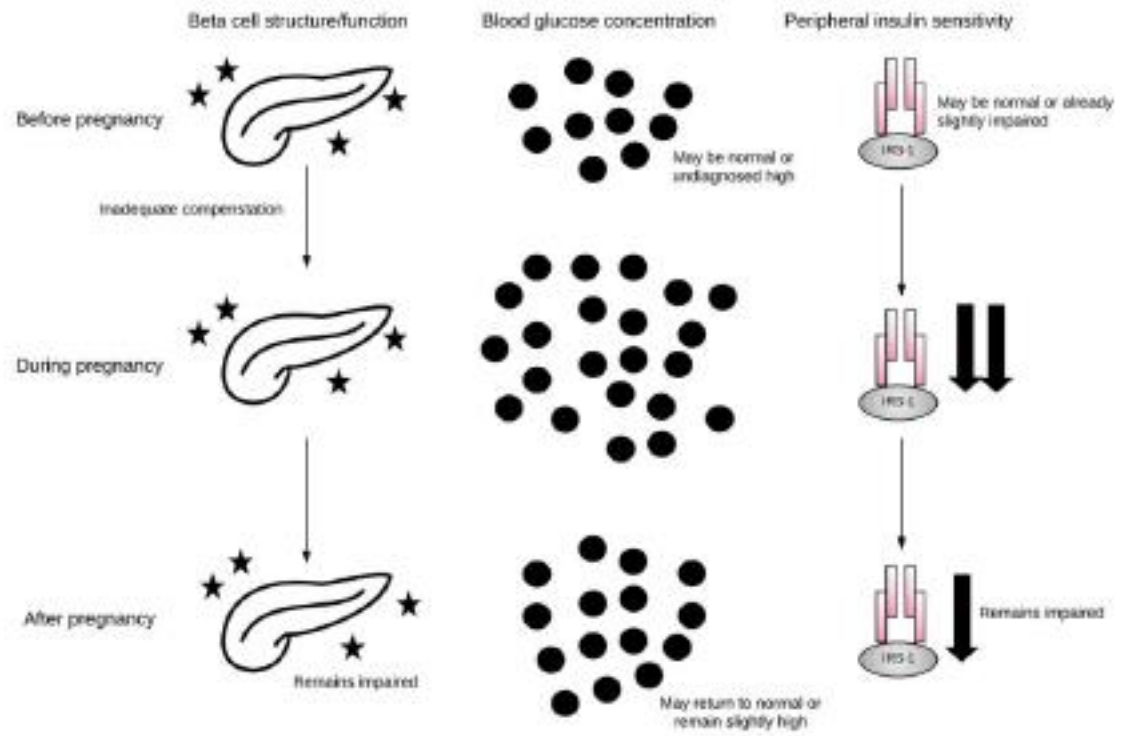

Figure 2 β-cell, blood glucose, and insulin sensitivity during normal pregnancy and GDM. During normal pregnancy, β-cells undergo hyperplasia and hypertrophy in order to meet the metabolic demands of pregnancy. Blood glucose rises as insulin sensitivity falls. Following pregnancy, β-cells, blood glucose, and insulin sensitivity return to normal. During gestational diabetes, β-cells fail to compensate for the demands of pregnancy, and, when combined with reduced insulin sensitivity, this results in hyperglycemia. Following pregnancy, β-cells, blood glucose, and insulin sensitivity may return to normal or may remain impaired on a pathway toward GDM in future pregnancy or T2DM. Pancreas image obtained from The Noun Project under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/), by artist Arif Fajar Vulianto.

Gestational diabetes

- Definition of gestational diabetes
- Incidence
- Risk factors
- Pathophysiology, Placentation
- Presentation, signs and symptoms
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- Special investigations
- Treatment
- Screening and prevention

- Failed conception (↑ HbA1c)
- Cardiovascular malformation
- Hyperglycaemia
- Glycosuria
- Recurrent UTI
- Polyhydramnion
- Subcutaneous fat layer
- Macrosomia
- PIH
- PET

Gestational diabetes

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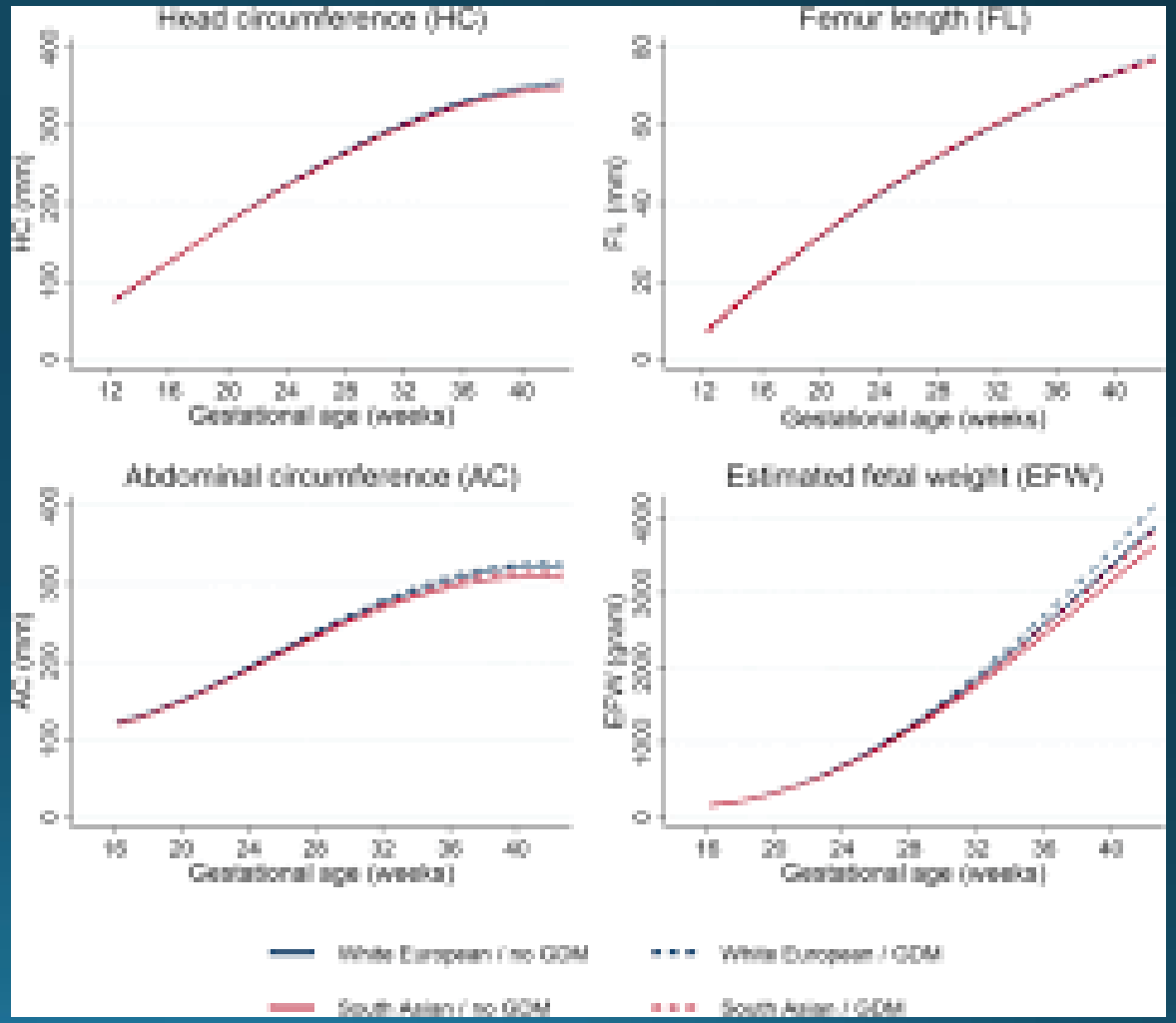

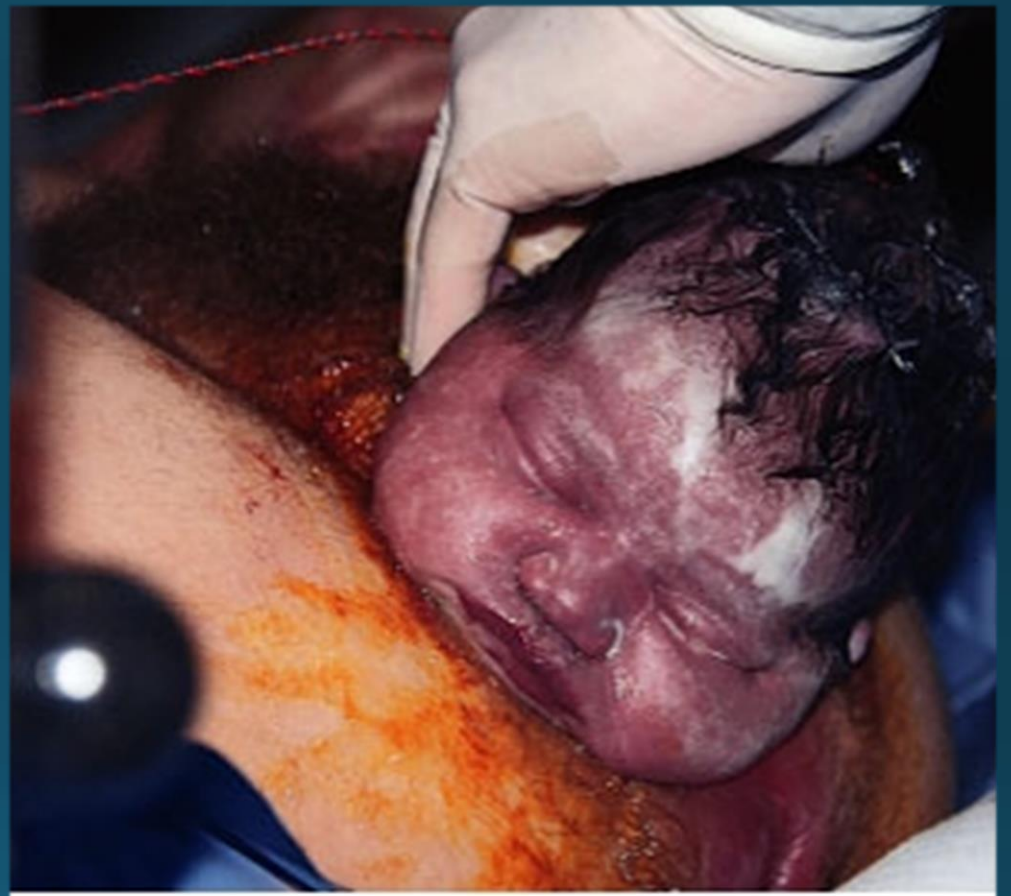

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Gestational diabetes

- Definition of gestational diabetes
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- Plows et al. Int. J. Mol. Sci. **2018**, 19, 3342; doi:10.3390/ijms19113342

Plows et al. Int. J. Mol. Sci. **2018**, 19, 3342; doi:10.3390/ijms19113342

Table 1. Various criteria for gestational diabetes mellitus (GDM) diagnosis using oral glucose tolerance test (OGTT).

Criteria	Pregnancies	Timing of OGTT	Steps	Glucose Load (g)	Glucose Threshold (mmol/L)			
					Fasting	1 h	2 h	3 h
O'Sullivan, 1964	All	24–28 weeks	2	100	5.0	9.2	8.1	6.9
WHO, 1999	All	24–28 weeks	1	75	7.0	—	7.8	—
American Diabetes Association (ADA), 2004	High and medium risk	14–18 weeks for high risk, 28–32 weeks for medium risk	2	100	5.3	10.0	8.6	7.8
National Institute for Health and Care Excellence (NICE), 2015	High risk	As early as possible	1	75	5.6	—	7.8	—
IADPSG, 2010 WHO, 2013 ADA, 2016	All	24–28 weeks	1	75	5.1	10.0	8.5	—

Gestational diabetes

- Definition of gestational diabetes
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- Biochemical markers: Se-glucose, fructosamine, HBA1c, OGTT
- Fetoplacental markers: growth (AC), amniotic fluid volume, subcutaneous fat, functional tests
- Assessment of diet, physical activity
- Regular BP-check, urinanalysis

Gestational diabetes

- Definition of gestational diabetes
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- Treatment
- Screening and prevention

- Nutritional counseling
- Calorie restriction to 25 kcal/kg/day
- Carbohydrates restriction to 180 g/day
- Bodyweight monitoring
- Moderate excercise
- Insulin therapy if 2h postprandial plasma-glucose >7,2 mmol/L
- Avoid prolonged pregnancy
- Breastfeeding

Gestational diabetes

- **Definition of gestational diabetes**
- **Incidence**
- **Risk factors**
- **Pathophysiology, Placentation**
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- **Special investigations**
- **Treatment**
- **Screening and prevention**

- Obstetric/Medical/Family history
- Prepregnancy check on glucose-metabolism
- Regular BP and urine-analysis
- Dietary advice
- Prepregnancy BMI normalisation

Preeclampsia

- **Definition of preeclampsia**
- **Incidence**
- **Risk factors**
- **Pathophysiology**
- **Placentation**
- **Presentation, signs and symptoms**
- **Fetal growth restriction**
- **Placental abruption**
- **Diagnosis**
- **Special investigations**
- **Treatment**

- BP>140/90 twice at resting 4 hours apart
- >0.5 g/L or >+ proteinuria in the absence of UTI (pyuria)
- Develops after 20th week and normalized within 3 months after delivery
- Carries high morbidity as opposed to Pregnancy Induced Hypertension

Preeclampsia

- Definition of preeclampsia
- Incidence
- Risk factors
- Pathophysiology
- Placentation
- Presentation, signs and symptoms
- Fetal growth restriction
- Placental abruption
- Diagnosis
- Special investigations
- Treatment

- 4-7% overall
- 75% occurs near term
- Complications

DIC/HELLP 10-20%
ARDS 2-5%
Abruption 1-5%
Eclampsia 1%
Renal failure 1%
Preterm delivery 15-60%
IUGR 10-25%
Perinatal death 1-2%

Preeclampsia

- Definition of preeclampsia
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- Special investigations
- Treatment
- Screening and prevention

- Primiparity
- Extremes of age
- Previous PET
- Primipaternity
- Limited sperm exposure
- Donor sperm or oocyte
- Chronic hypertension
- Diabetes
- Autoimmune diseases
- Smoking
- Family history of PET

Preeclampsia

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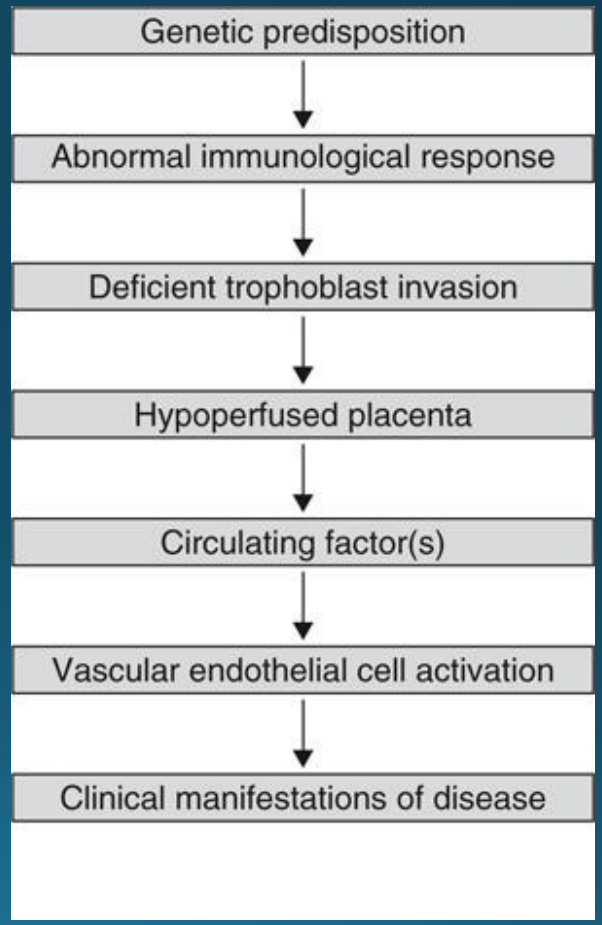
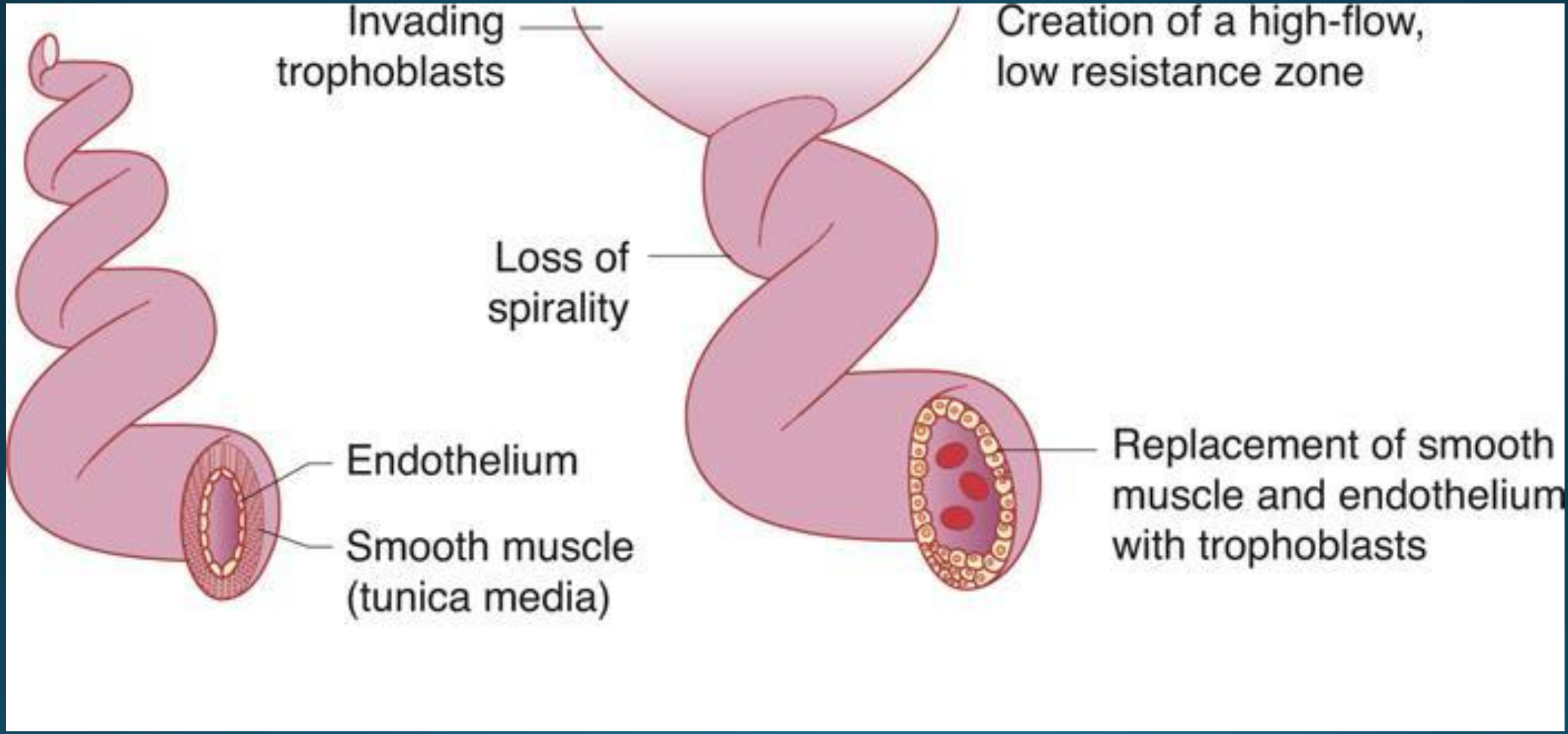
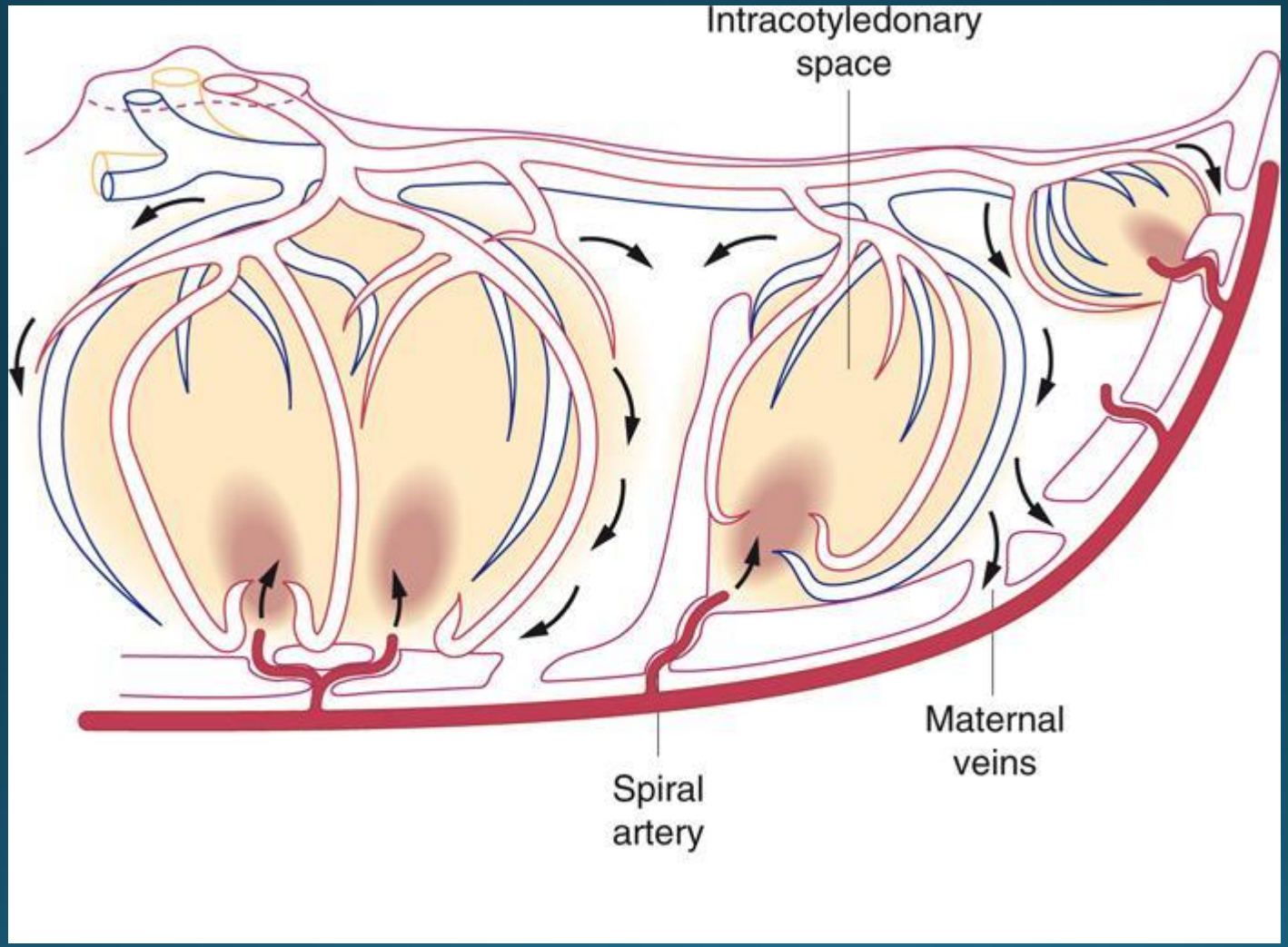
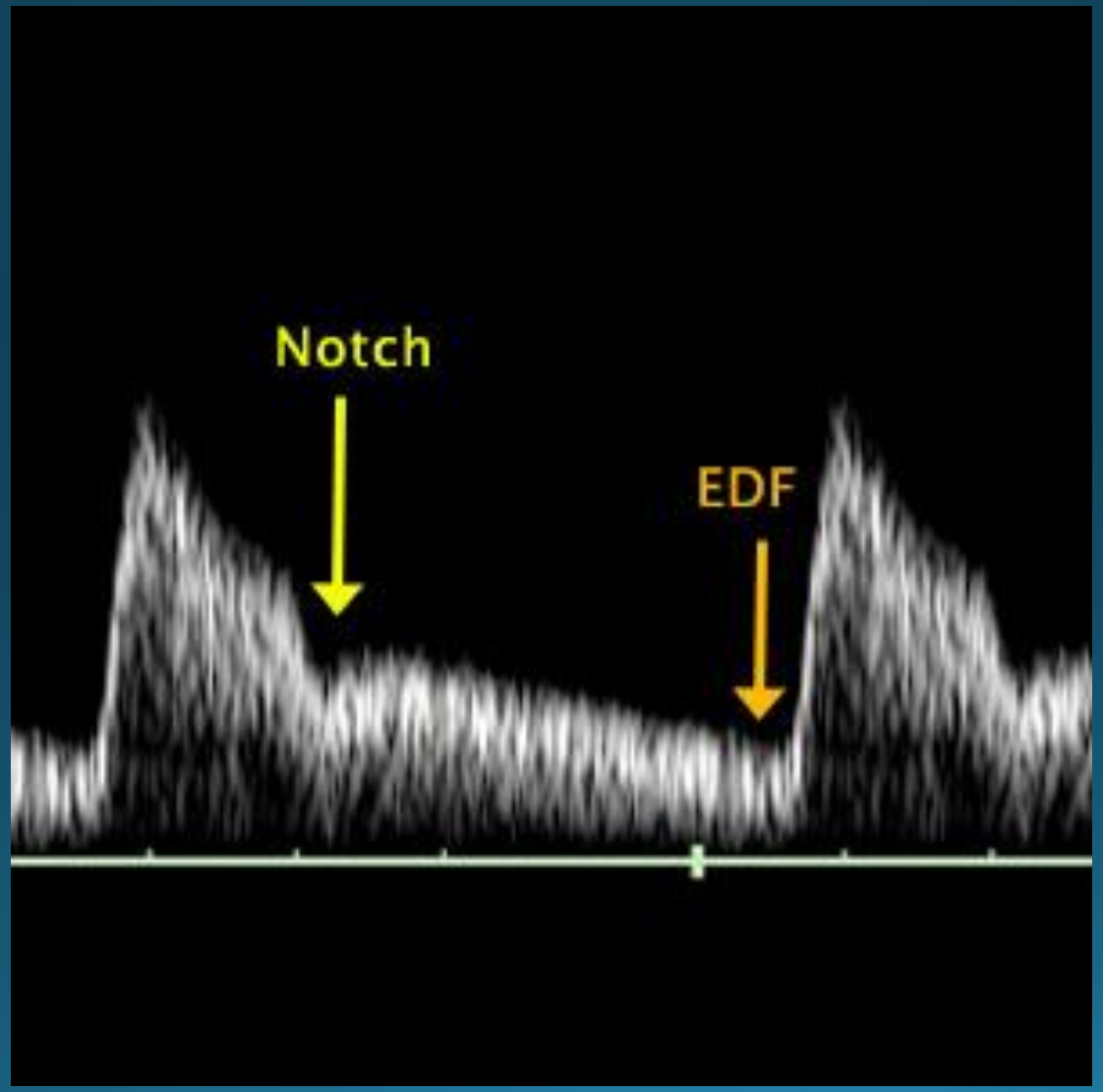



Invading trophoblasts
Creation of a high-flow, low resistance zone
Loss of spirality
Endothelium
Smooth muscle (tunica media)
Replacement of smooth muscle and endothelium with trophoblasts


Intracotyledonary space
Maternal veins
Spiral artery

Uterine artery notching



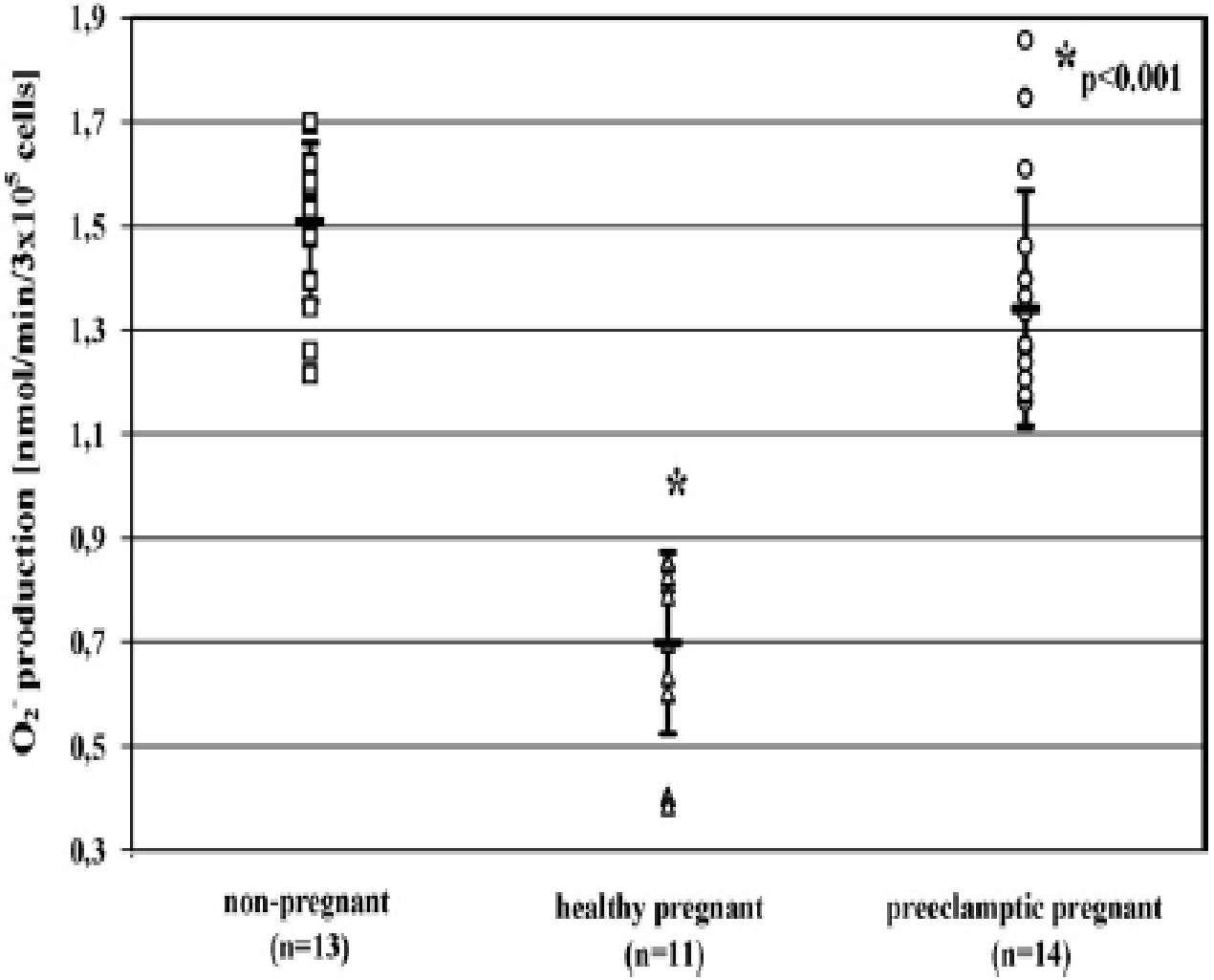


Fig. 1. PDBu-stimulated mean superoxide-anion production of granulocytes separated from non-pregnant, healthy pregnant and preeclamptic pregnant women. Mean values ± S.D. are shown. *$p < 0.001$, healthy pregnant versus non-pregnant and preeclamptic pregnant women.

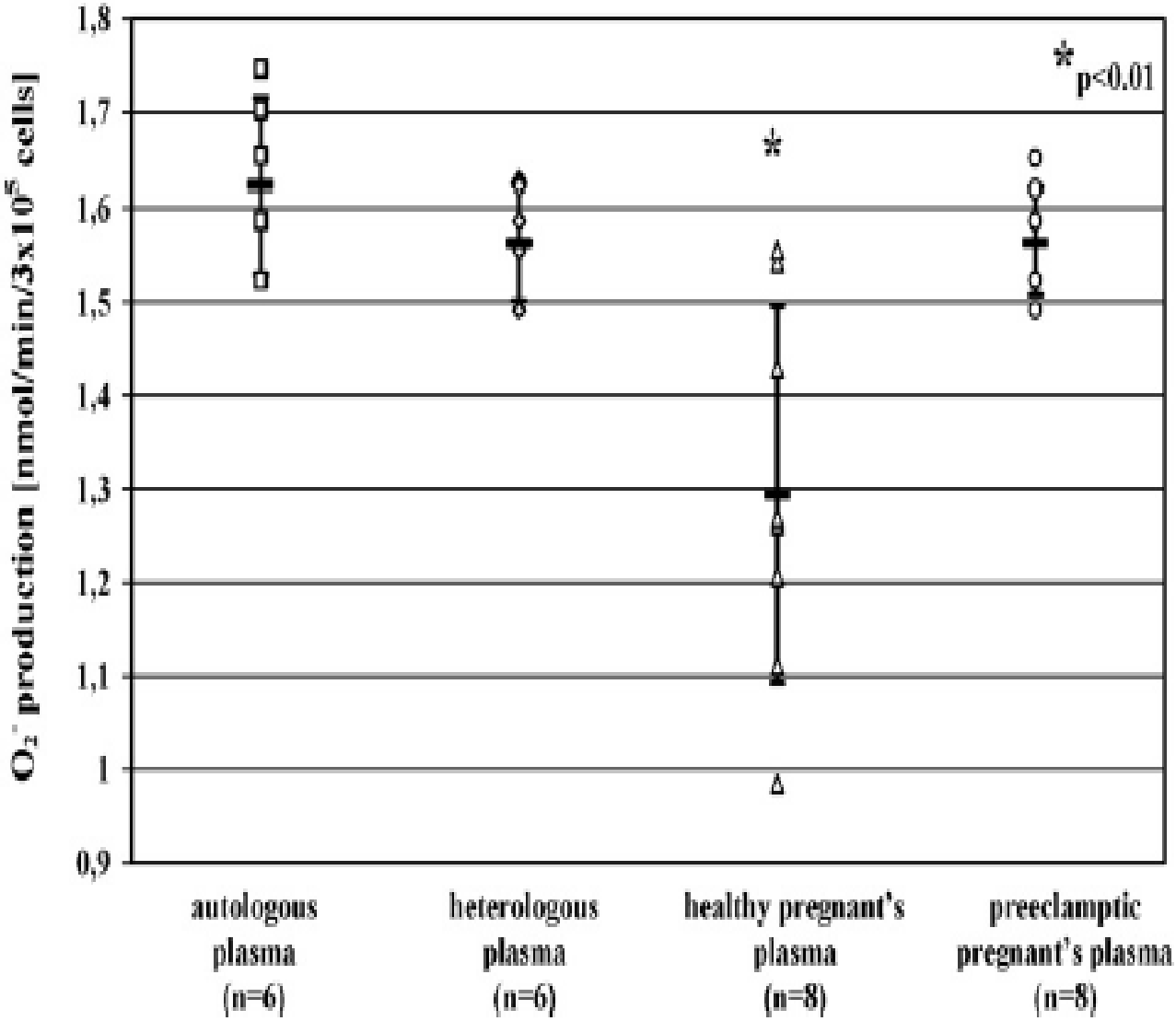


Fig. 3. Effects of plasma samples on PDBu-stimulated superoxide-anion production by granulocytes. Mean values ± S.D. are demonstrated. $^*p < 0.01$ healthy pregnant plasma versus autologous plasma.

Preeclampsia

- **Definition of preeclampsia**
- **Incidence**
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- **Screening and prevention**

- Uterine artery notch
- ↑ β-hCG
- Increased weight-gain
- Oedema, ↑Htc, „normal" Hb
- Failed midtrimester ↓BP
- ↑BP, proteinuria
- Hyperreflexia, clonus, eclamptic fit

Frontal headache,
Epigastric pain,
Visual disturbances

Preeclampsia

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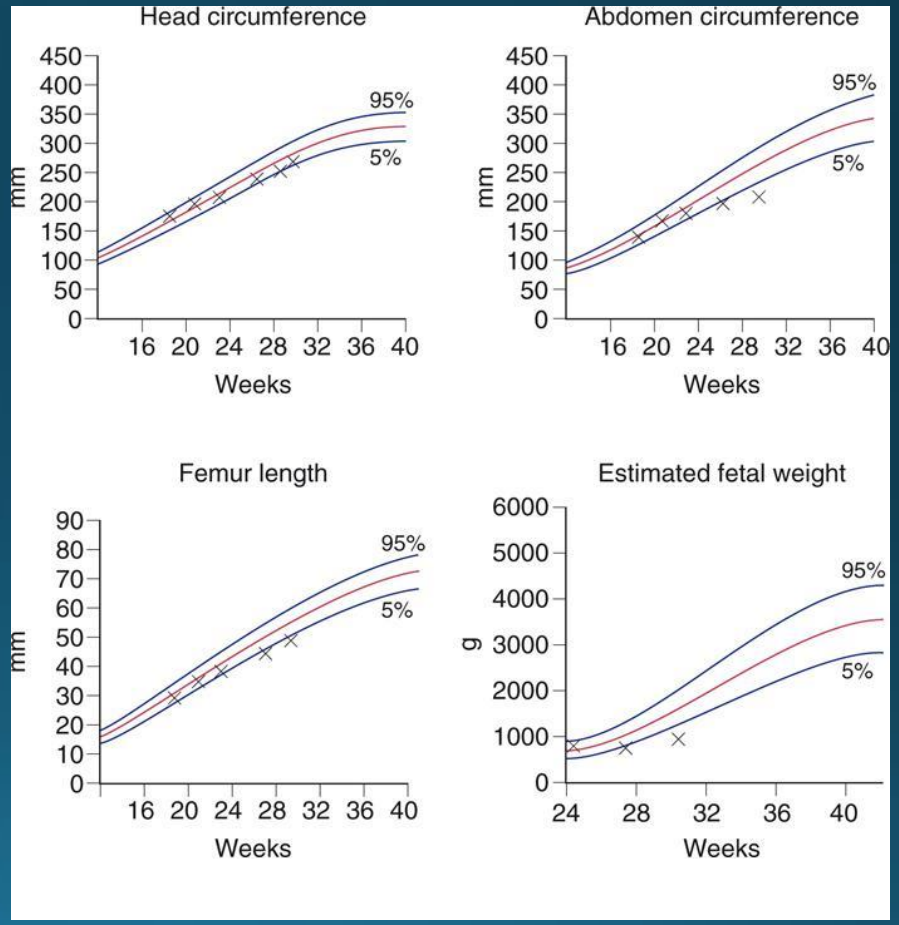

Preeclampsia

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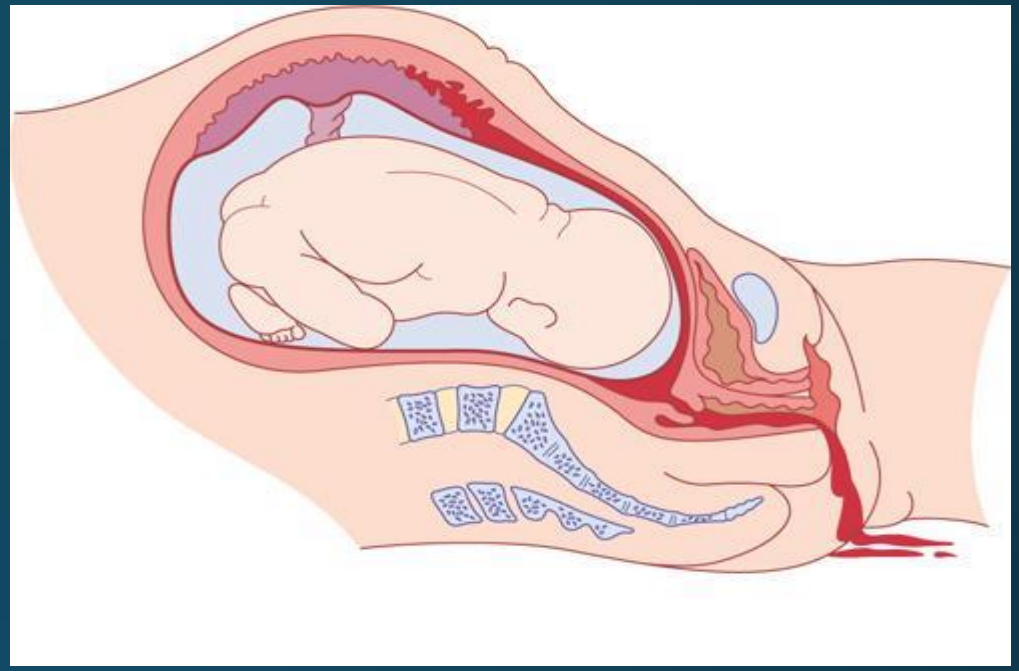

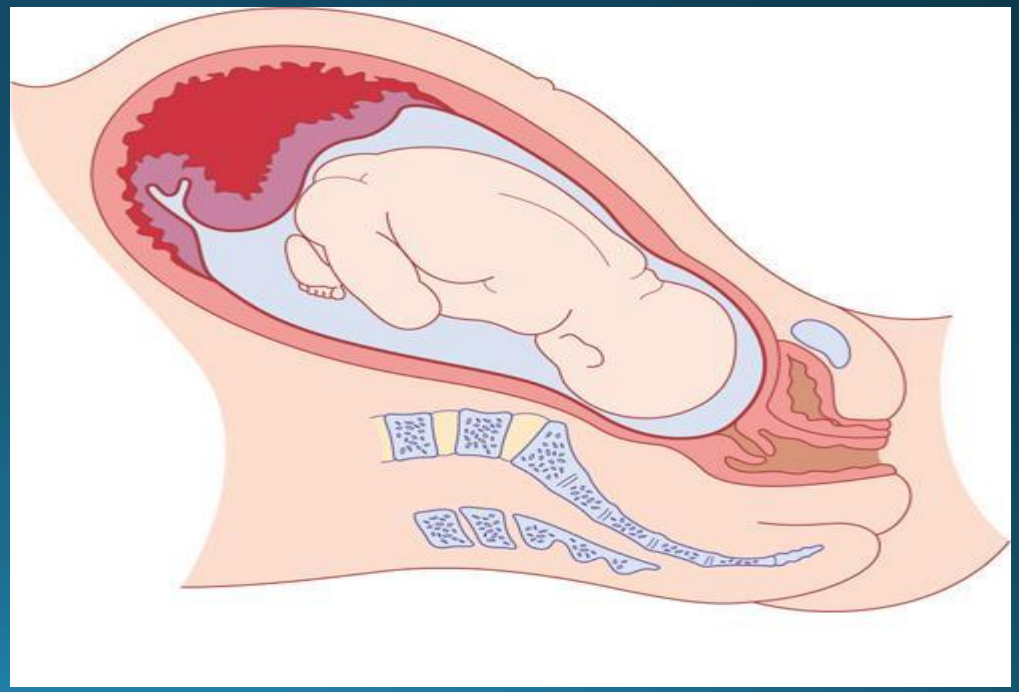

Preeclampsia

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- Diagnosis
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- Screening and prevention

- BP>140/90 twice at resting 4 hours apart
- >0.5 g/L or >+ proteinuria in the absence of UTI (pyuria)

Frontal headache,

Epigastric pain,

Visual disturbances

Preeclampsia

- Definition of preeclampsia
- Incidence
- Risk factors
- Pathophysiology, Placentation
- Presentation, signs and symptoms
- Fetal growth restriction
- Placental abruption
- Diagnosis
- Special investigations
- Treatment
- Screening and prevention

- Physical markers: Wt, BP
- Haematological markers: Hb, Htc, Plt, APTT, INR, FDP, D-dimer
- Biochemical markers: Proteinuria, Se-uric acid, Urine Ca/Crea, GOT, Se-Alb, Urine output
- Fetoplacental markers

Preeclampsia

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- No fluid restriction
- Protein supplementation (p.o., i.v.)
- Antihypertensive Tx
  - Antidopaminerg
  - Ca-channel blockers
  - α-β-blockers
- Hospitalisation, bedrest

- **Volumen expansion (iv.Albumin/HAES)**
- **Antihypertensive Tx (Urapidil, Hydralazin)**
- **Anticonvulsant Tx ($MgSO_4$)**

Preeclampsia

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- Screening and prevention

- Obstetric/Medical/Family history
- First trimester biochemical screening
- First trimester uterine artery doppler
- Baseline biochemistry
- Regular BP and urine-analysis

- Dietary advice
- Ca-supplementation
- Vitamins C and E
- Fish-oil
- Aspirin

Haemorrhagic complications

- Definitions
- Epidemiology
- Causes
- Classification
- Diagnosis
- Treatment
- Prevention

- Antepartum haemorrhage (APH)

Revealed or concealed bleeding after 20 weeks

- Postpartum haemorrhage (PPH)

Loss of >500mL from the genital tract within 24 hrs (primary PPH)

Or within 3mths (secondary PPH)

Haemorrhagic complications

- Definitions
- Epidemiology
- Causes
- Classification
- Diagnosis
- Treatment
- Prevention

- 2-3% frequency
- Increasing
- 3rd most common cause of maternal mortality
- Increases with parity
- Increases with age
- Increases with CS frequency

Haemorrhagic complications

- Definitions
- Epidemiology
- Causes
- Classification
- Diagnosis
- Treatment
- Prevention

- Abruption
- Placenta praevia
- Vasa praevia
- Trauma of birth-canal
- Atony
- Abnormal placentation
- Inversion
- Cervical cancer
- Haemostatic disorders

Haemorrhagic complications

- Definitions
- Epidemiology
- Causes
- Classification
- Diagnosis
- Treatment
- Prevention

- Abruption

Revealed and concealed

- Placenta praevia

Low lying, marginal and central

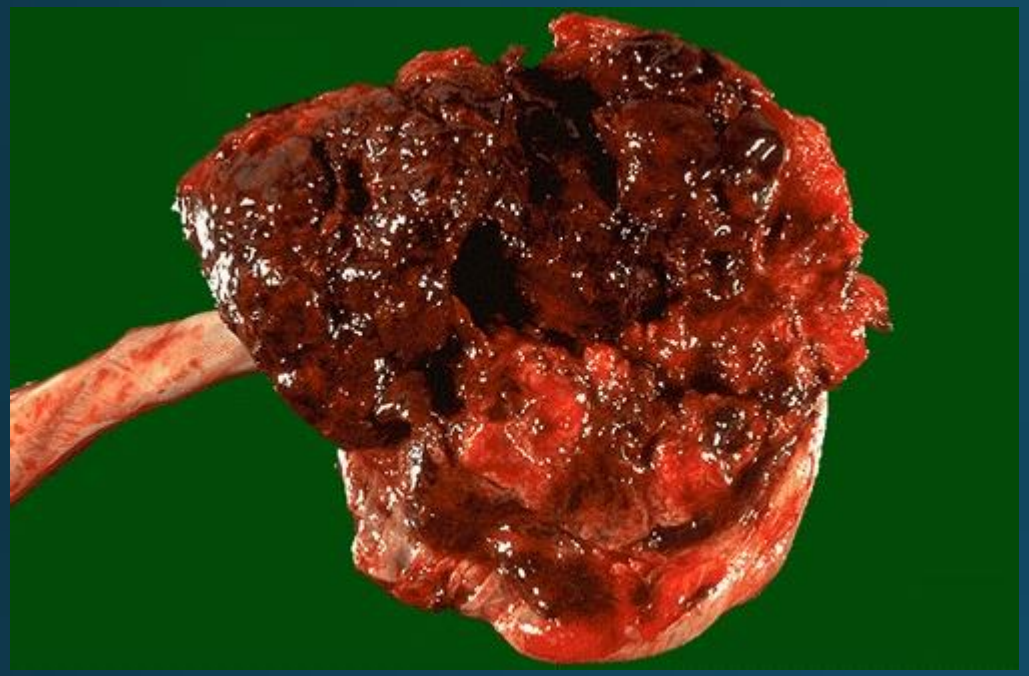
- Adherent placenta

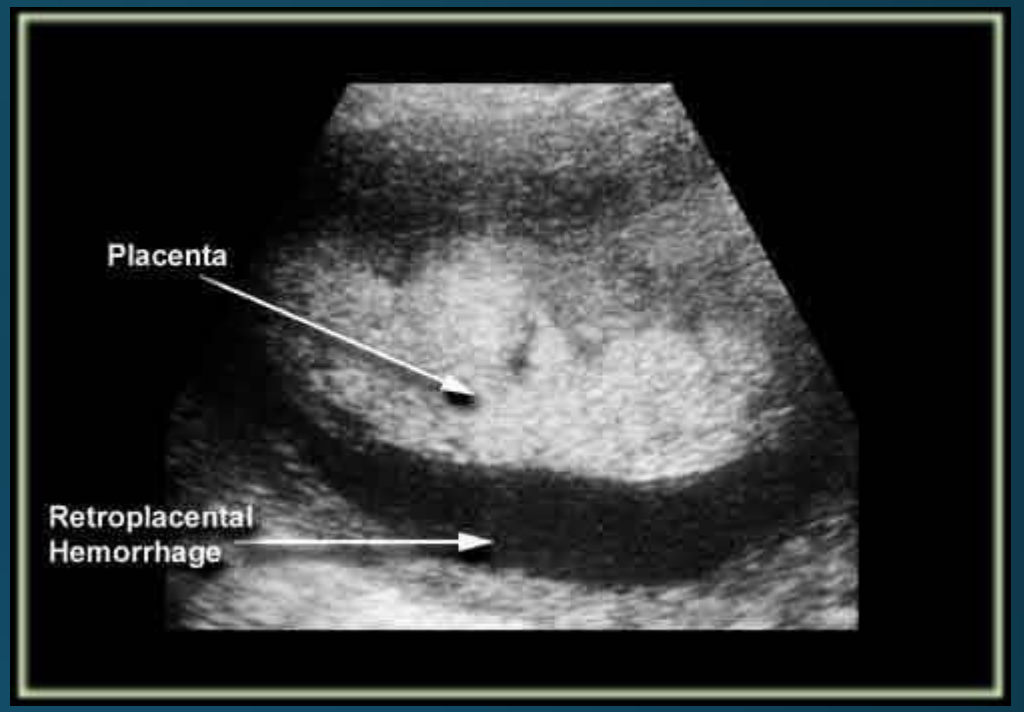
Placenta accreta, increta and percreta

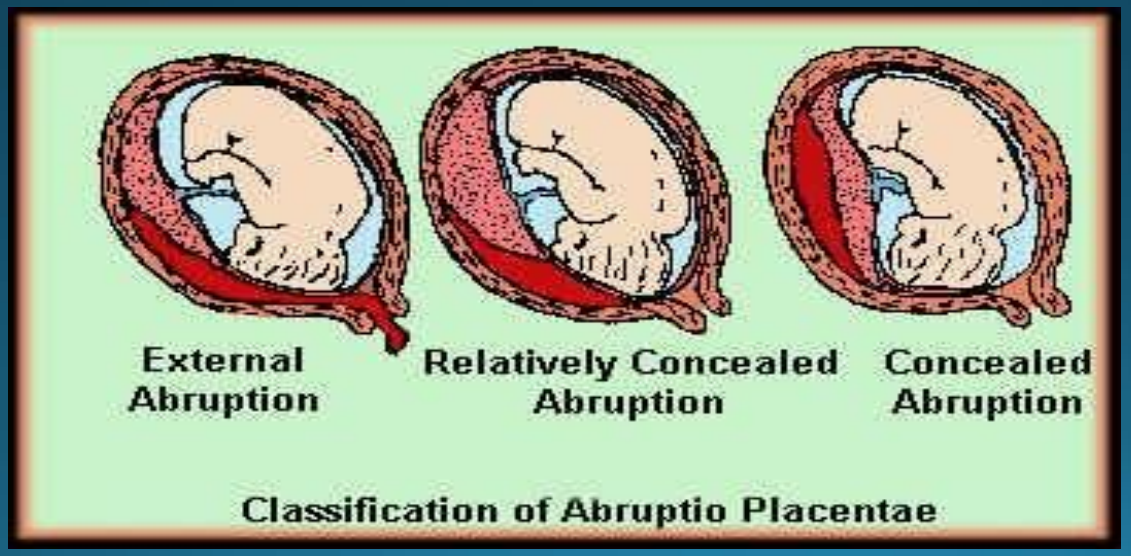
- Haemostatic disorders

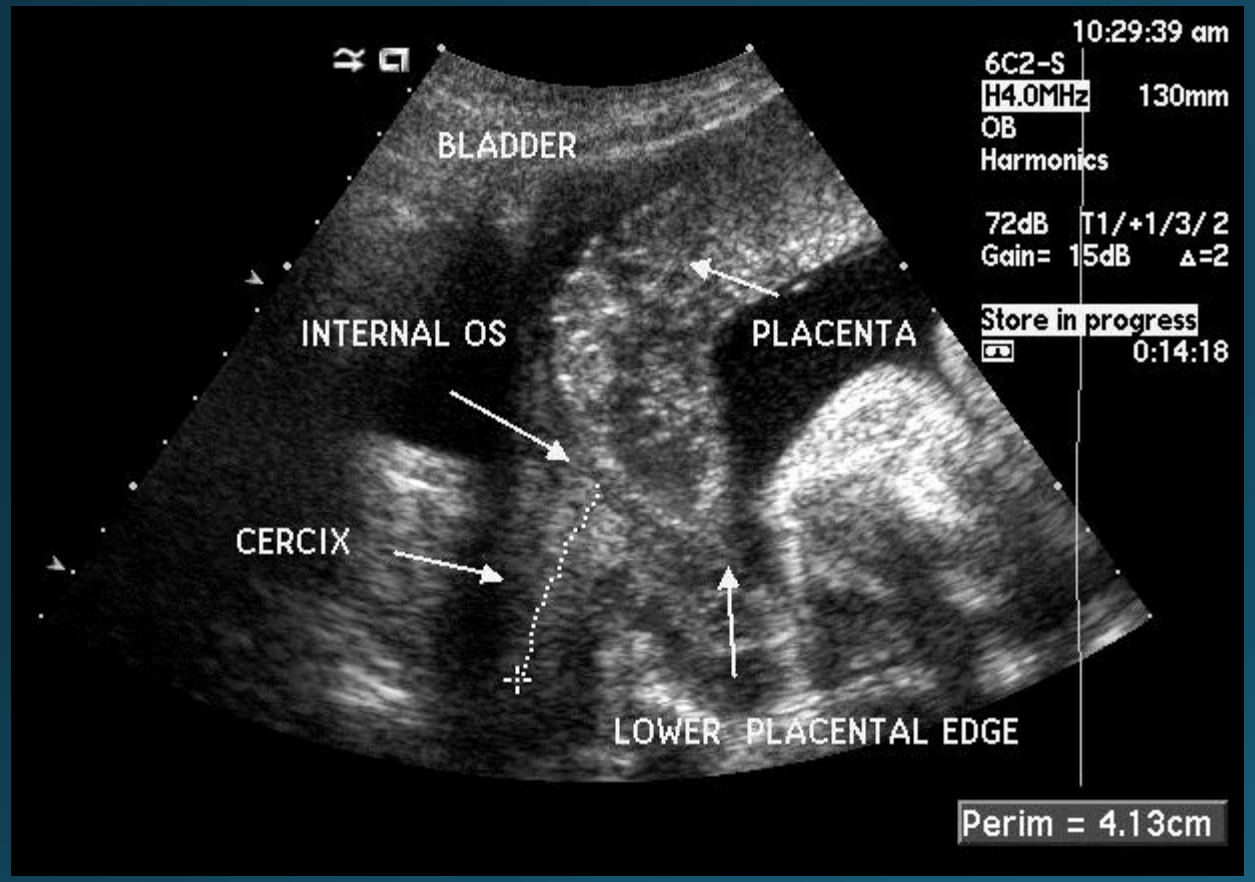
Coagulopathy, thrombocytopathy, vasculopathy
Inherited, acquired

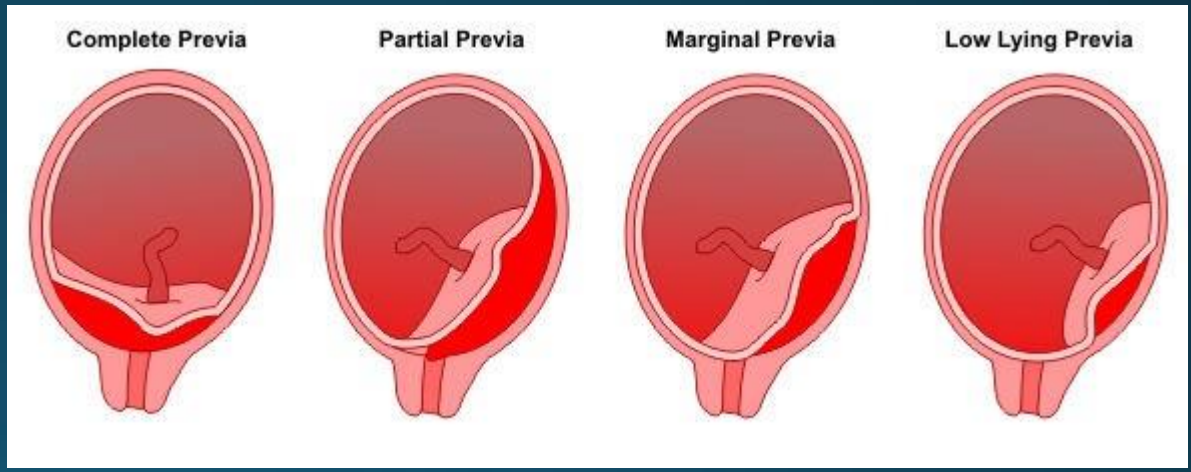
General, gender-specific

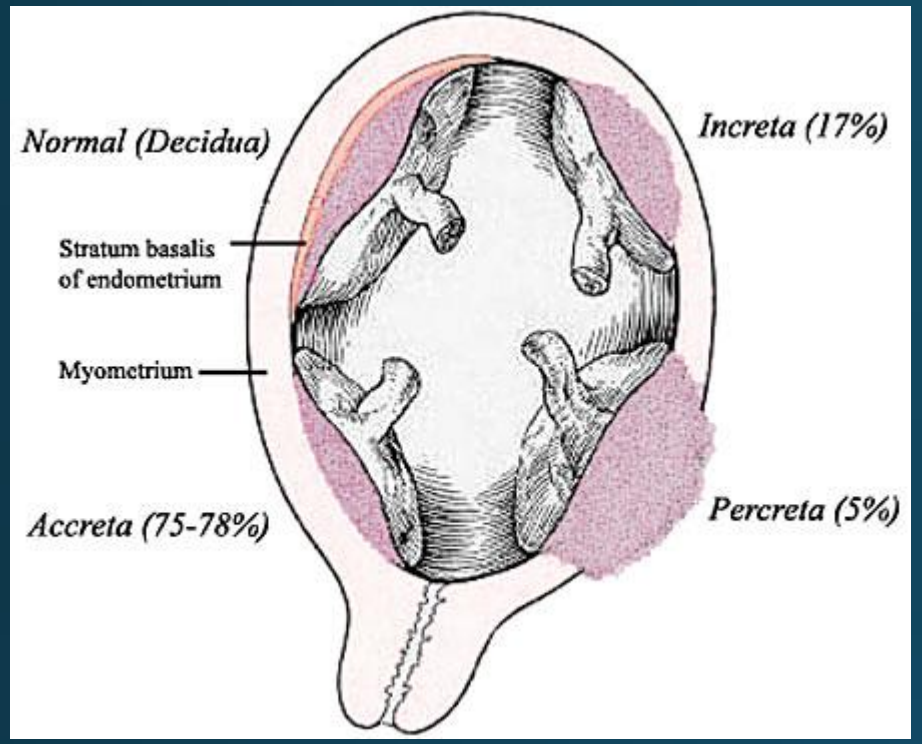


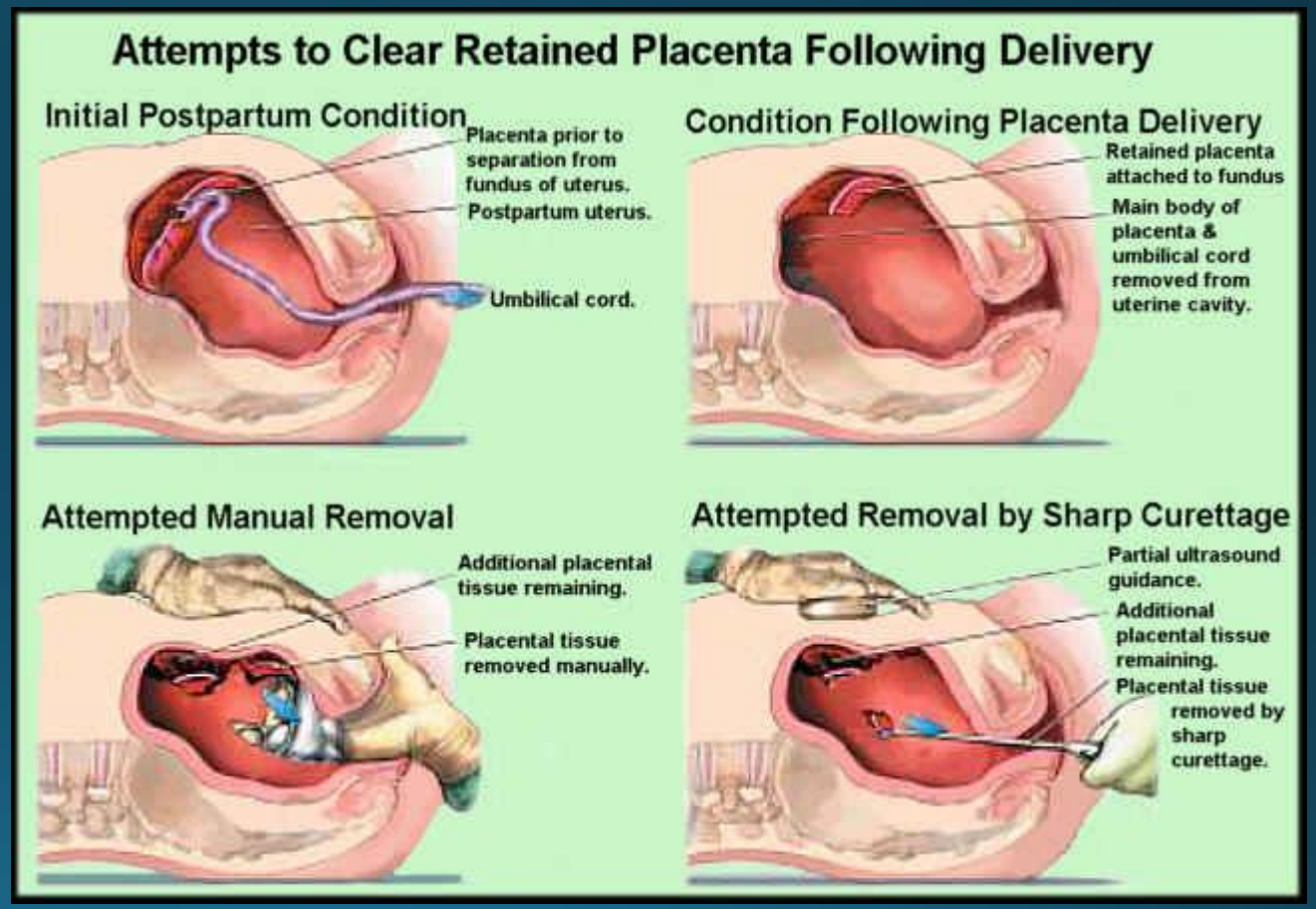

Placenta
Retroplacental
Hemorrhage

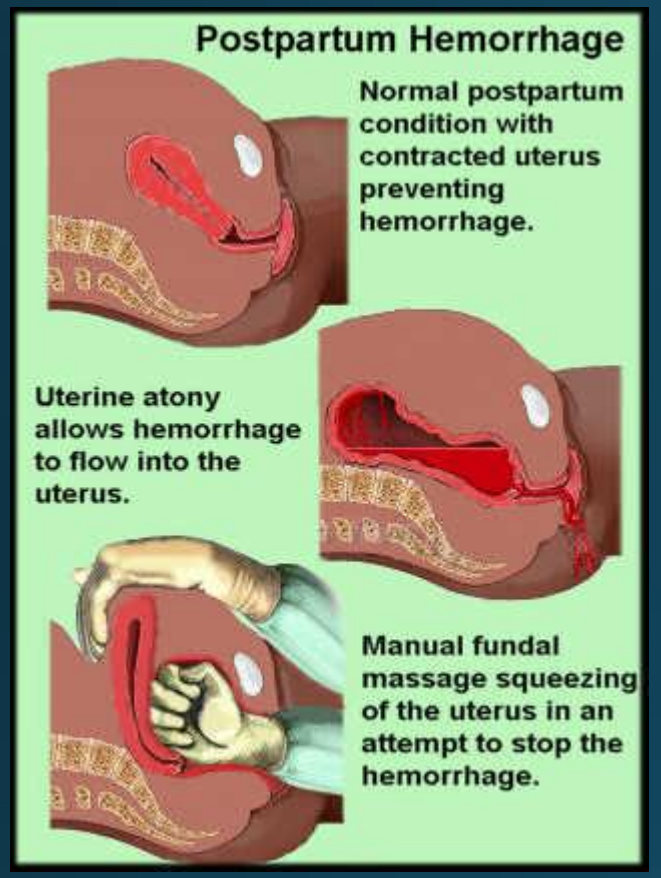

External
Abruption
Relatively Concealed
Abruption
Concealed
Abruption
Classification of Abruptio Placentae

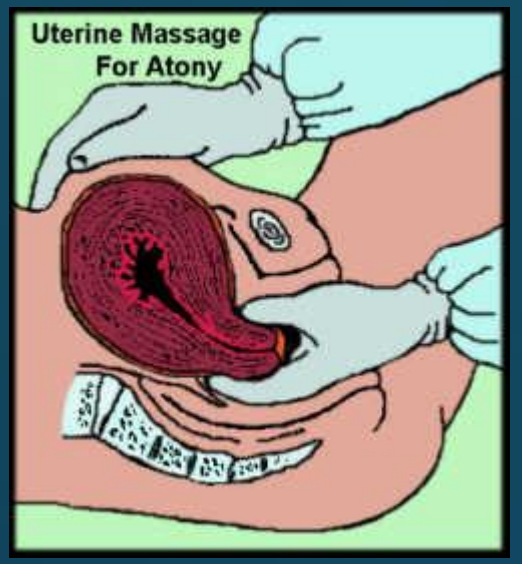

10:29:39 am
6C2-S
H4.0MHz
130mm
OB
Harmonics
72dB T1/+1/3/2
Gain= 15dB Δ=2
Store in progress
0:14:18
BLADDER
INTERNAL OS
PLACENTA
CERCIX
LOWER PLACENTAL EDGE
Perim = 4.13cm

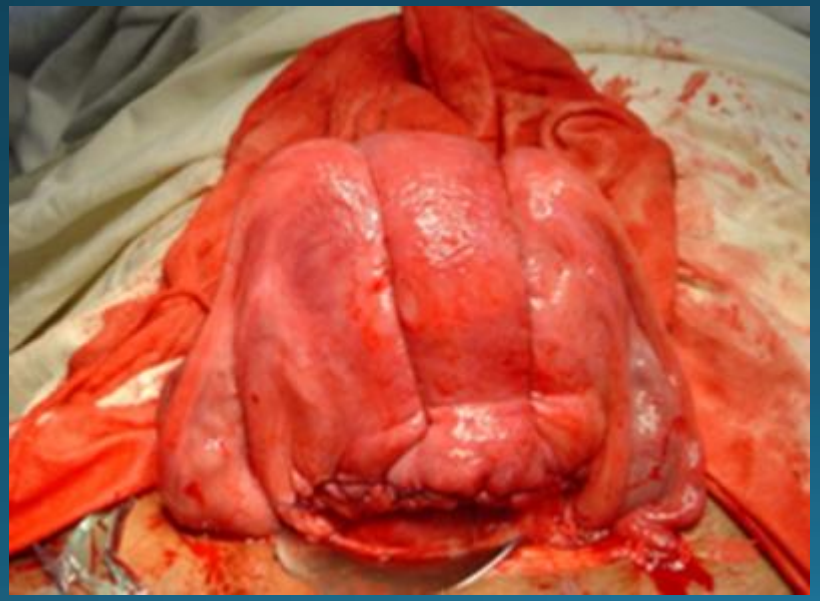

Complete Previa
Partial Previa
Marginal Previa
Low Lying Previa

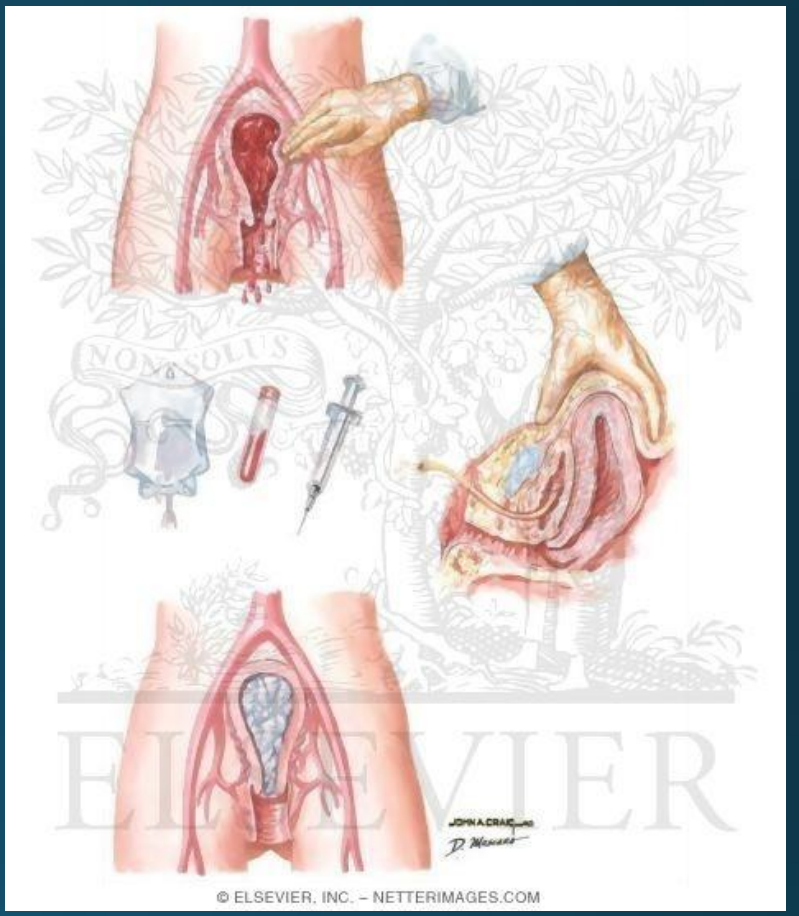

Normal (Decidua)
Increta (17%)
Stratum basalis of endometrium
Myometrium
Accreta (75-78%)
Percreta (5%)


Attempts to Clear Retained Placenta Following Delivery
Initial Postpartum Condition
Placenta prior to separation from fundus of uterus.
Postpartum uterus.
Umbilical cord.
Condition Following Placenta Delivery
Retained placenta attached to fundus
Main body of placenta & umbilical cord removed from uterine cavity.
Attempted Manual Removal
Additional placental tissue remaining.
Placental tissue removed manually.
Attempted Removal by Sharp Curettage
Partial ultrasound guidance.
Additional placental tissue remaining.
Placental tissue removed by sharp curettage.


Postpartum Hemorrhage
Normal postpartum condition with contracted uterus preventing hemorrhage.
Uterine atony allows hemorrhage to flow into the uterus.
Manual fundal massage squeezing of the uterus in an attempt to stop the hemorrhage.


Uterine Massage For Atony

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Haemorrhagic complications

- Definitions
- Epidemiology
- Classification
- Causes
- Diagnosis
- Treatment
- Prevention

- Quick check of four Ts (Tone,Tissue,Trauma,Thrombin)
- Amount of lost blood
- Physical properties of lost blood
- Previous episodes of bleeding
- Uterine tone and irritability
- Painful or painless
- Relation between loss and general state
- Precipitating factor
- Clotting screen

Haemorrhagic complications

- Definitions
- Epidemiology
- Classification
- Causes
- Diagnosis
- Treatment
- Prevention

- Summon help at most senior level
- O_2 mask
- 2x14-gauge iv.lines
- FBC+clotting screen
- X-match 6 units (massive haemorrhage)
- Fluid (christalloid) resuscitation with CVP control
- Foley catheter insertion for diuresis monitoring
- Transfuse ASAP (O Rh.neg. if at hand)
- FFP, Cryoprecipitate, Platelet
- Eliminate cause

Haemorrhagic complications

- Definitions
- Epidemiology
- Classification
- Causes
- Diagnosis
- Treatment
- Prevention

- Early US, regular US-follow-up
- Detailed history taking to identify risk factors
- Folic acid and Iron supplementation
- Continuous risk assessment
- Careful antenatal follow-up
- Prophylactic measures (smoking and drug-use cessation, avoid prolonged labour, X-match, large bore iv.line, avoid hyperstimulation, atony prevention, active management of 3rd stage, careful check for retained placental tissues, haematological consultation)

F1-level and the risk of major obstetric haemorrhage

- Charbit et al. J Thromb Haemost 2007
- N=50 parturients (out of 128 cases with uterine atony)
- PPH= >4 units packed cells, >5 g/dL Hb-decrease

- Results:
- Fibrinogen-level was the only significant predictor of PPH
- Every 1g/L decrease of F1 level increased OR of PPH by 2,7 95%CI (1,7-4,2)
- Initial F1 > 4 g/L had a negative predictive value of 80% for PPH
- Initial F1 < 2 g/L had a positive predictive value of 100% for PPH

Further retrospective data

- Cortet et al. Br J Anaesth 2012
- N= 738 vaginal birth, frequency of PPH as a function of F1
- F1 < 2g/L PPH OR=12 95%CI (2,6-52)

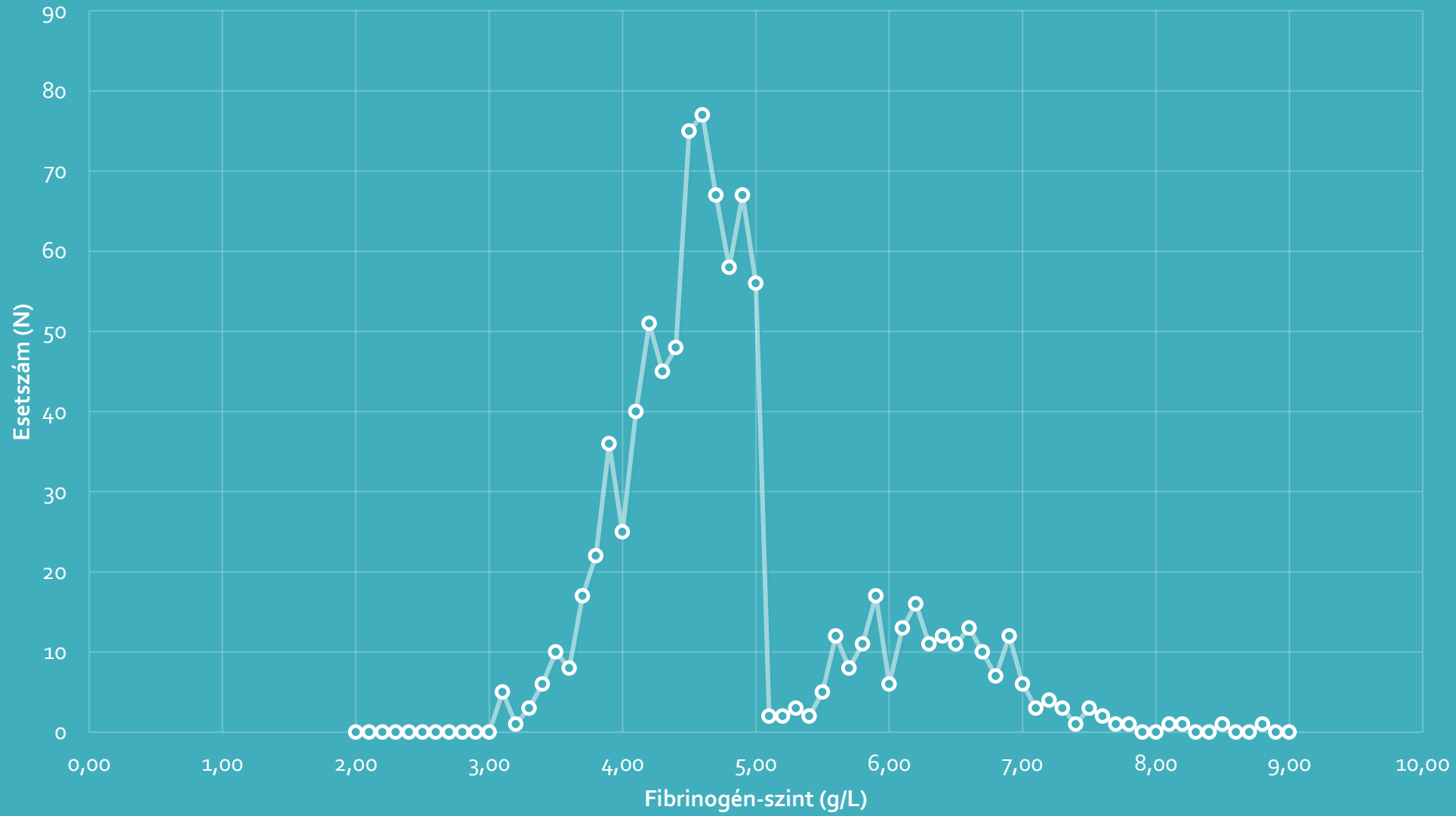
- De Lloyd et al. Int J Obstet Anaesth 2011
- N= 456 cases of PPH, F1 nadir compared between cases requiring >4 units RBC and <4 units RBC
- F1 nadirs 2,2 g/L and 3,8 g/L, respectively

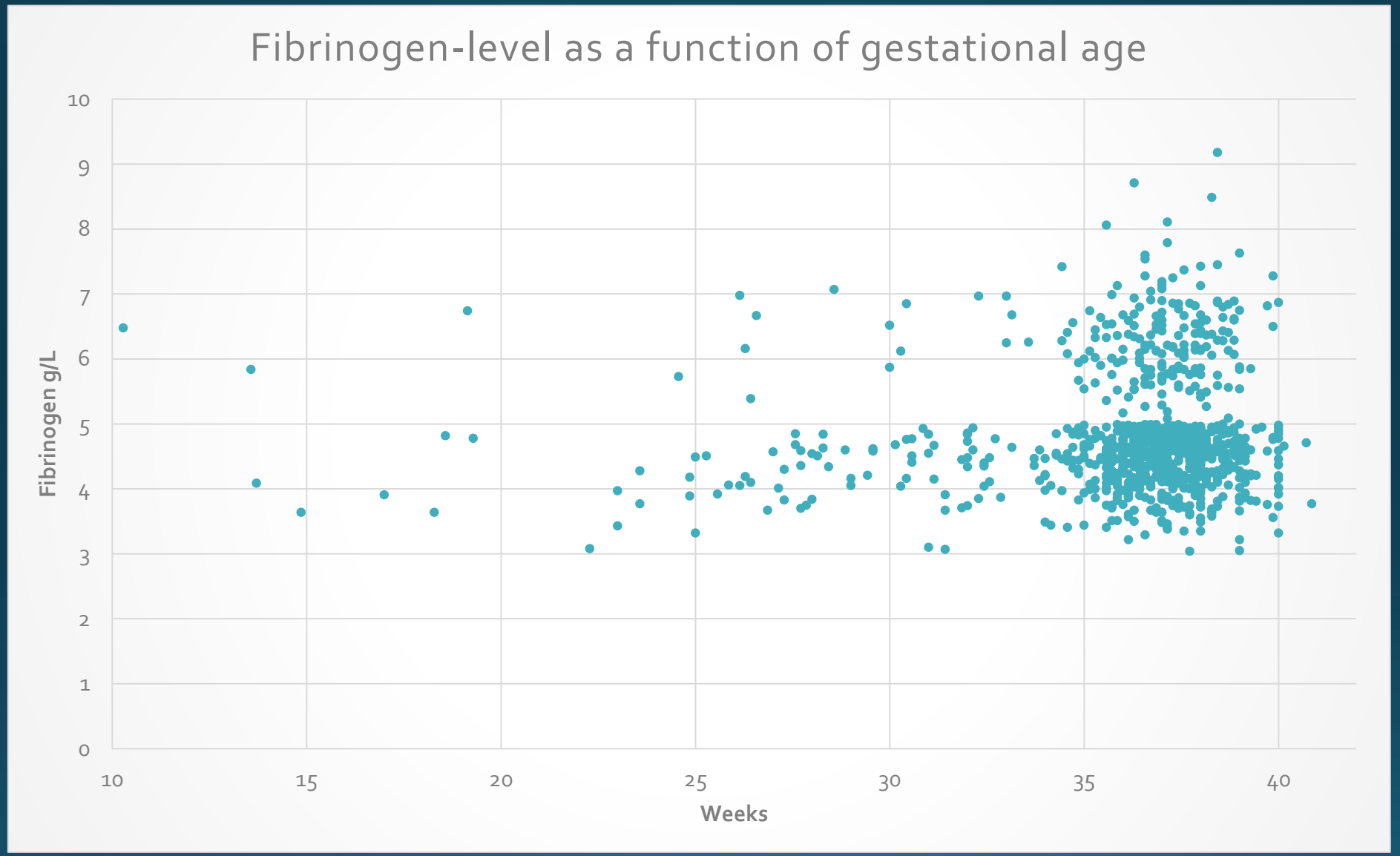
Hungarian F1 reference data

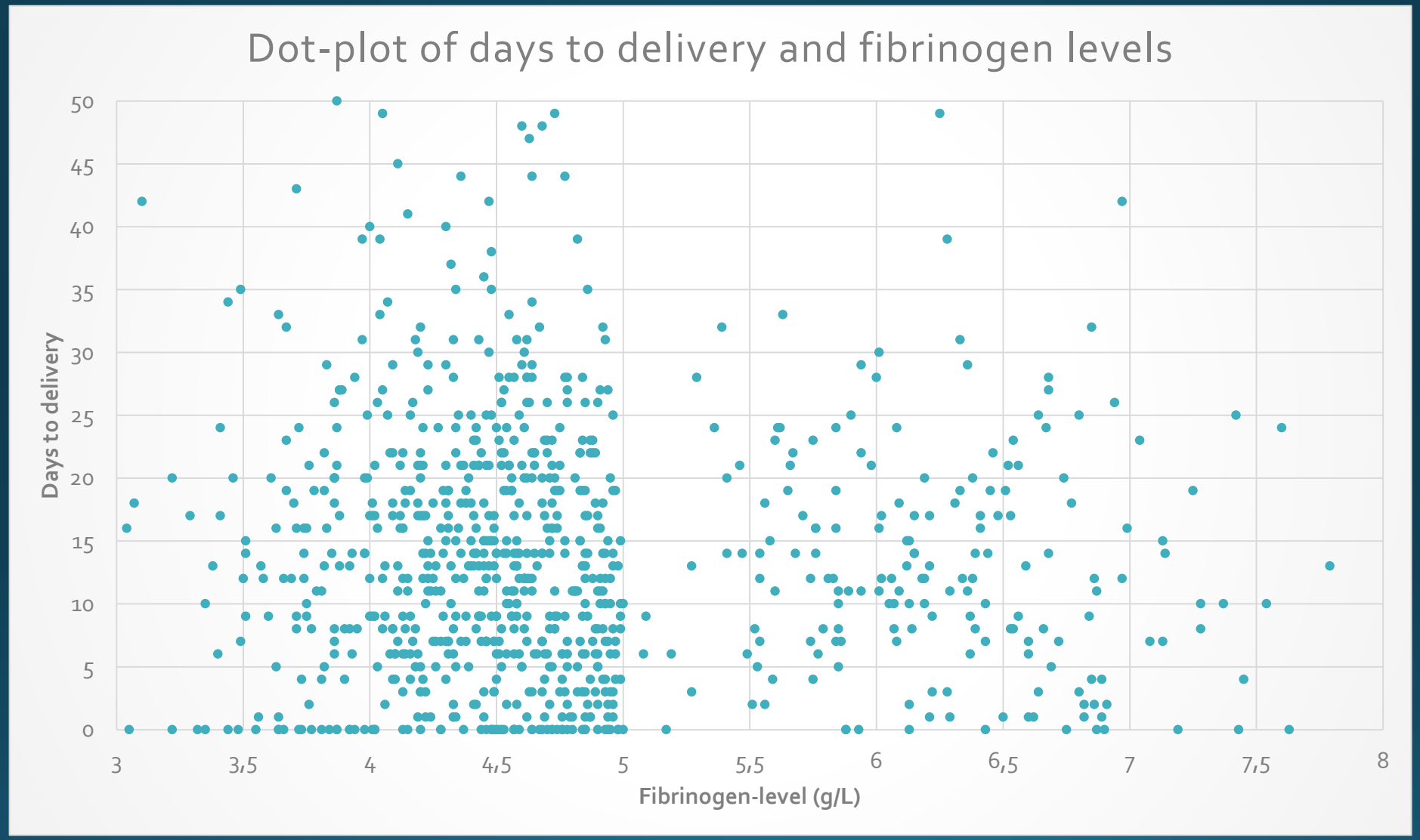
- Losonczy H et al. Thromb Res 2013
- 83 pregnant women (55 healthy) , F1 and D-dimer measurements at 16,26,36 weeks

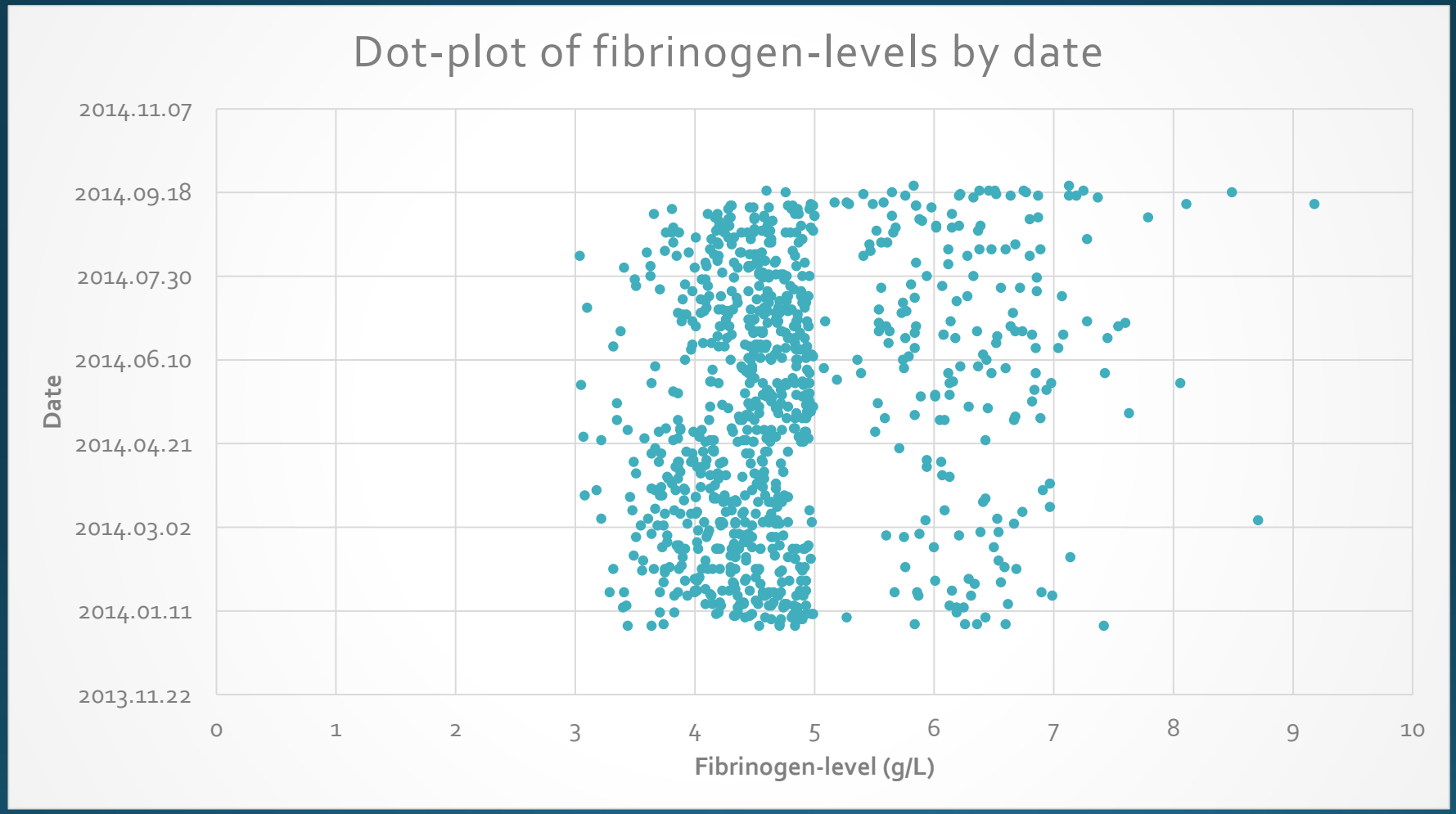
- Results:
- 16th week F1 4,2 g/L
- 26th week F1 5,0 g/L
- 36th week F1 6,0 g/L
- D-dimer 250-300-600 ng/mL

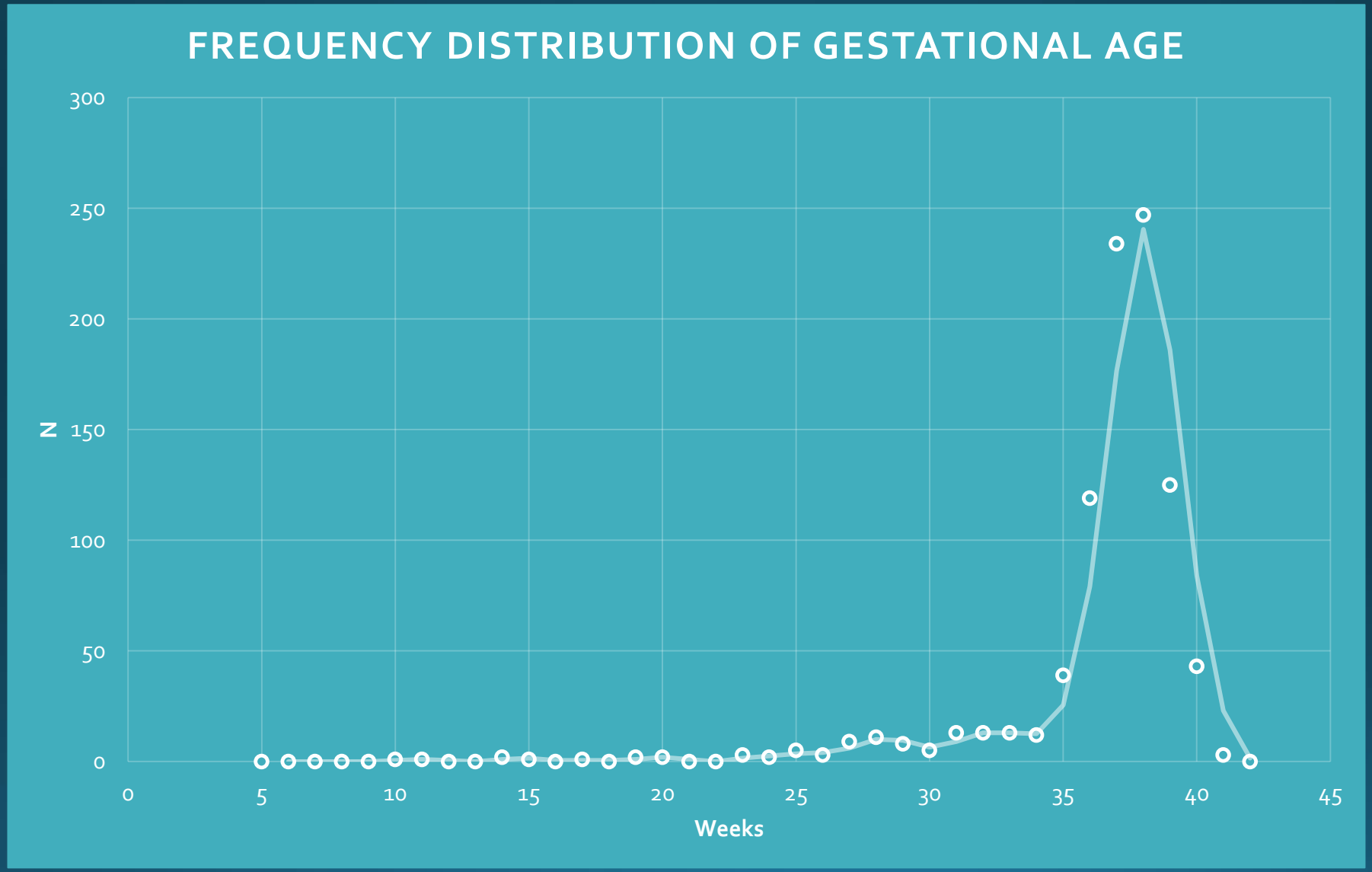
FREQUENCY DISTRIBUTION OF FIBRINOGEN-LEVELS

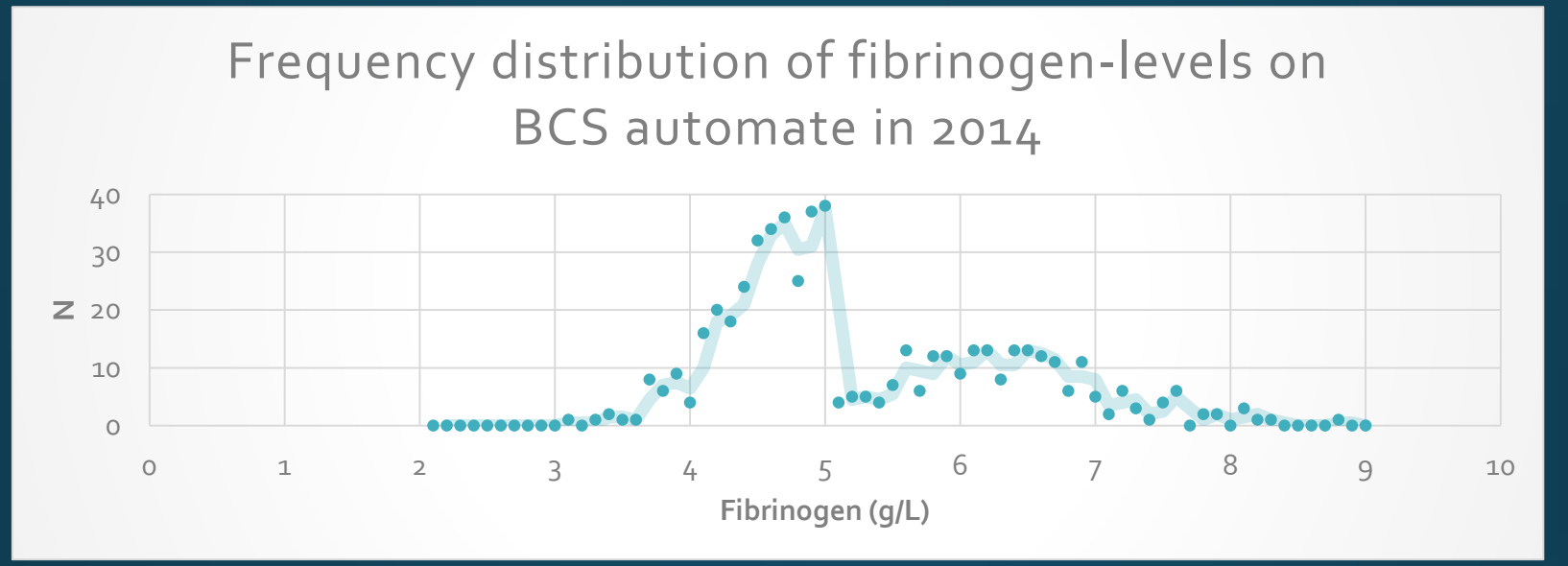


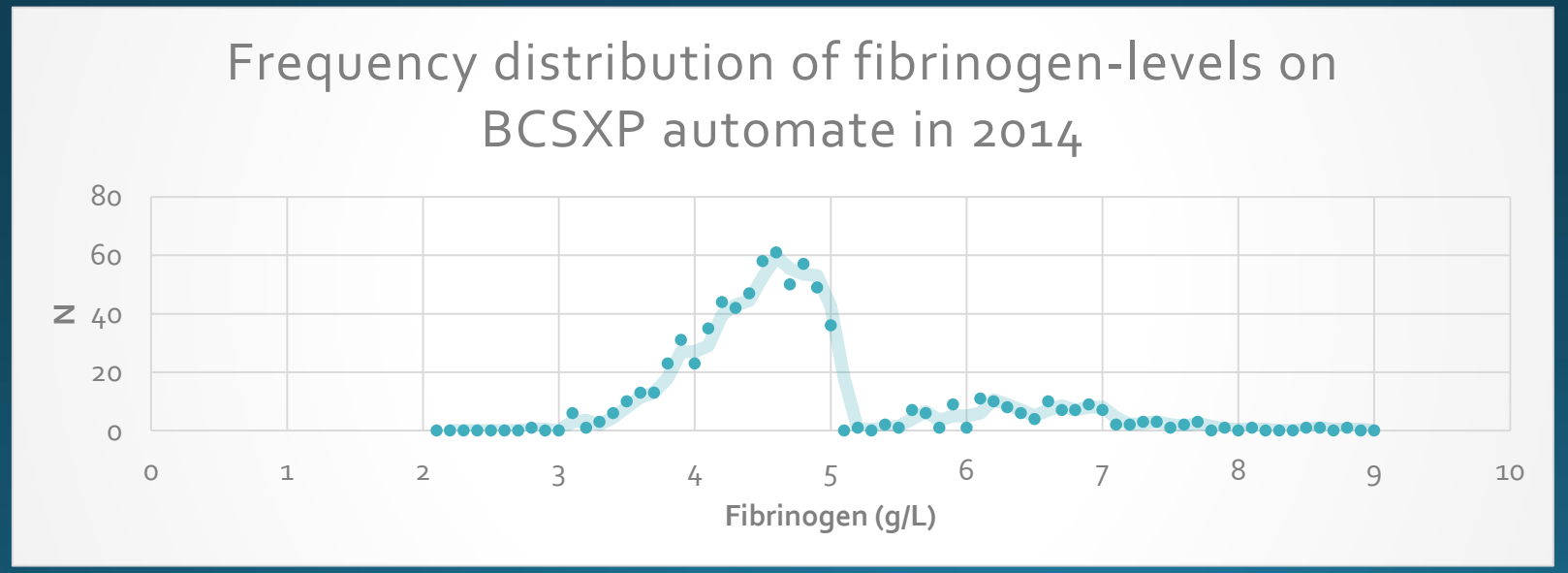

Fibrinogen-level as a function of gestational age
Fibrinogen g/L
0
1
2
3
4
5
6
7
8
9
10
10
15
20
25
30
35
40
Weeks

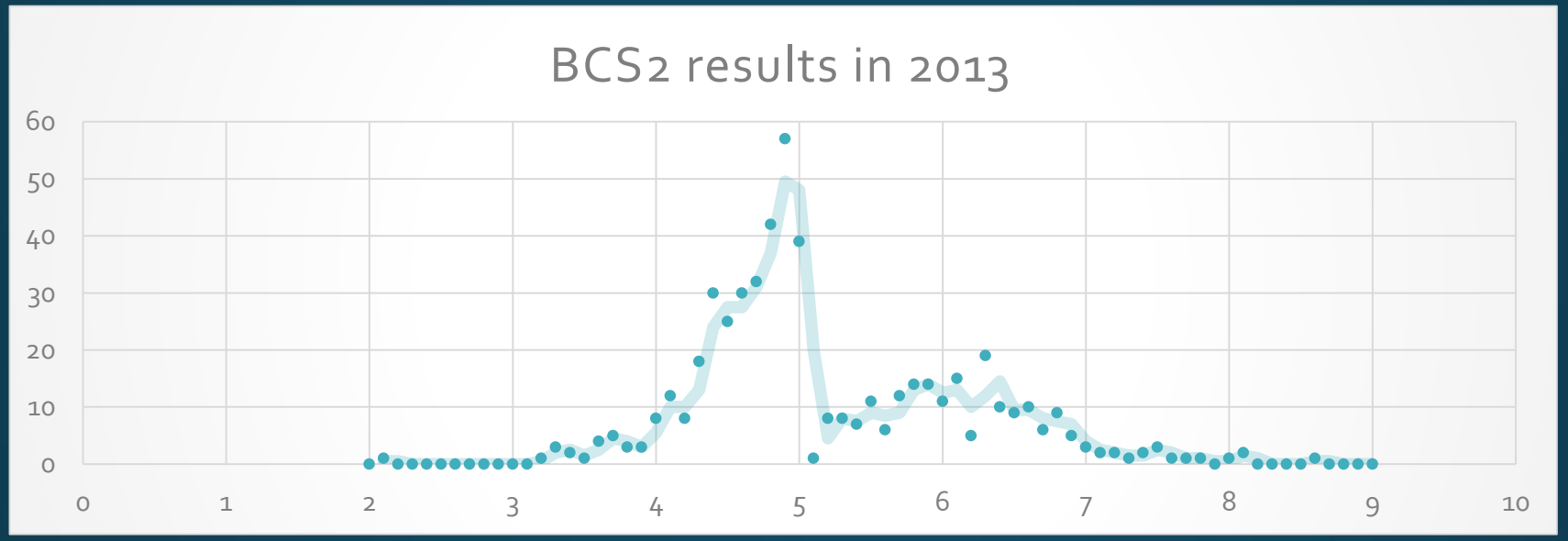

Dot-plot of days to delivery and fibrinogen levels
Days to delivery
0
5
10
15
20
25
30
35
40
45
50
3
3,5
4
4,5
5
5,5
6
6,5
7
7,5
8
Fibrinogen-level (g/L)

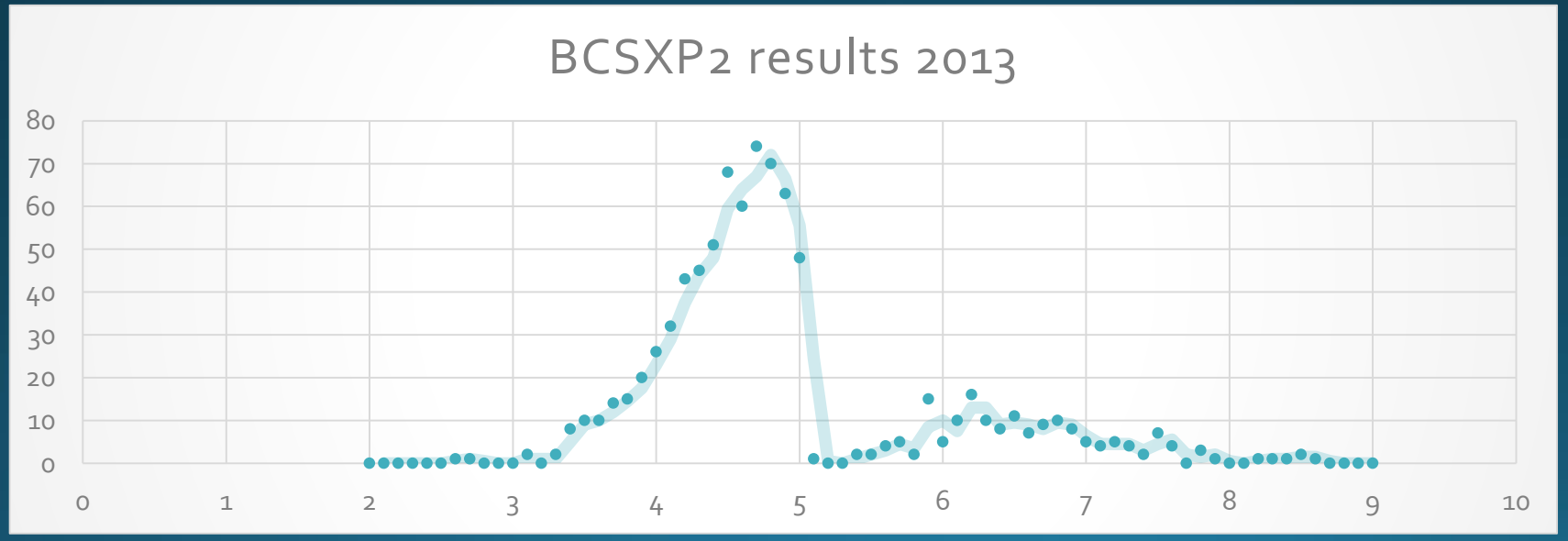

Dot-plot of fibrinogen-levels by date
2014.11.07
2014.09.18
2014.07.30
2014.06.10
2014.04.21
2014.03.02
2014.01.11
2013.11.22
Date
0
1
2
3
4
5
6
7
8
9
10
Fibrinogen-level (g/L)


FREQUENCY DISTRIBUTION OF GESTATIONAL AGE
300
250
200
150
100
50
0
N
0
5
10
15
20
25
30
35
40
45
Weeks

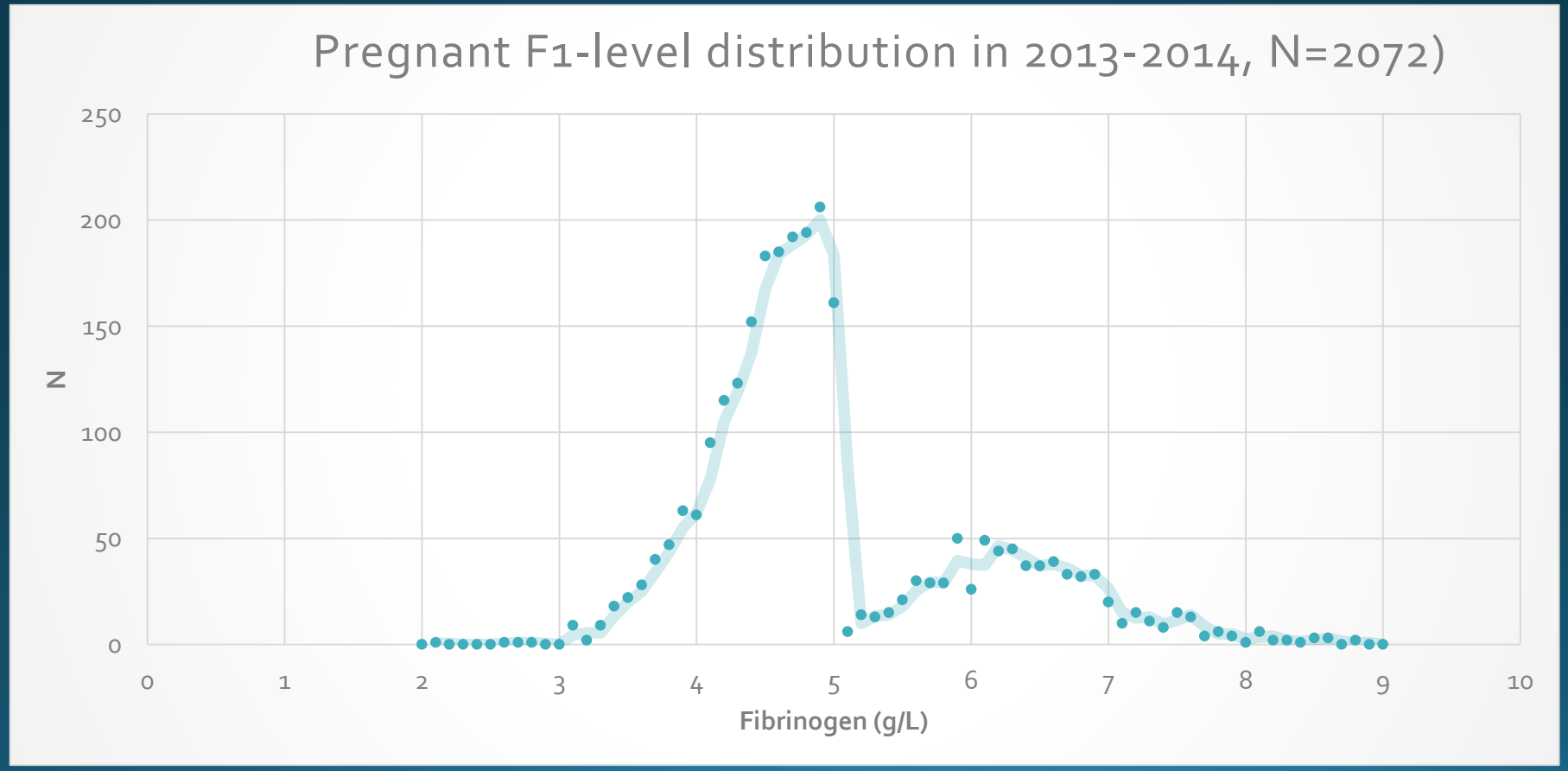

Frequency distribution of fibrinogen-levels on BCS automate in 2014
N
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
Fibrinogen (g/L)


Frequency distribution of fibrinogen-levels on BCSXP automate in 2014
N
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
10
Fibrinogen (g/L)

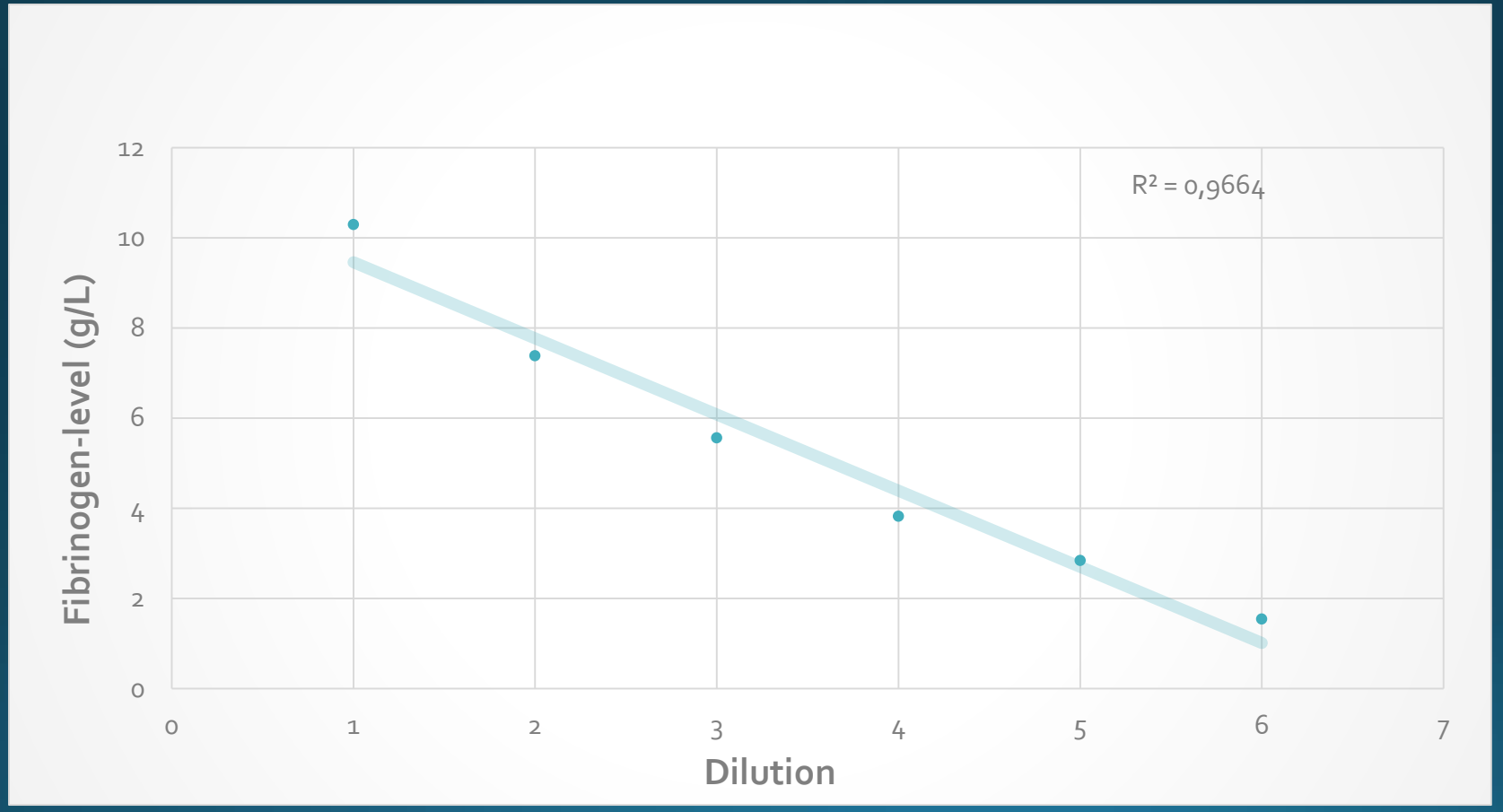

BCS2 results in 2013
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10


BCSXP2 results 2013
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10

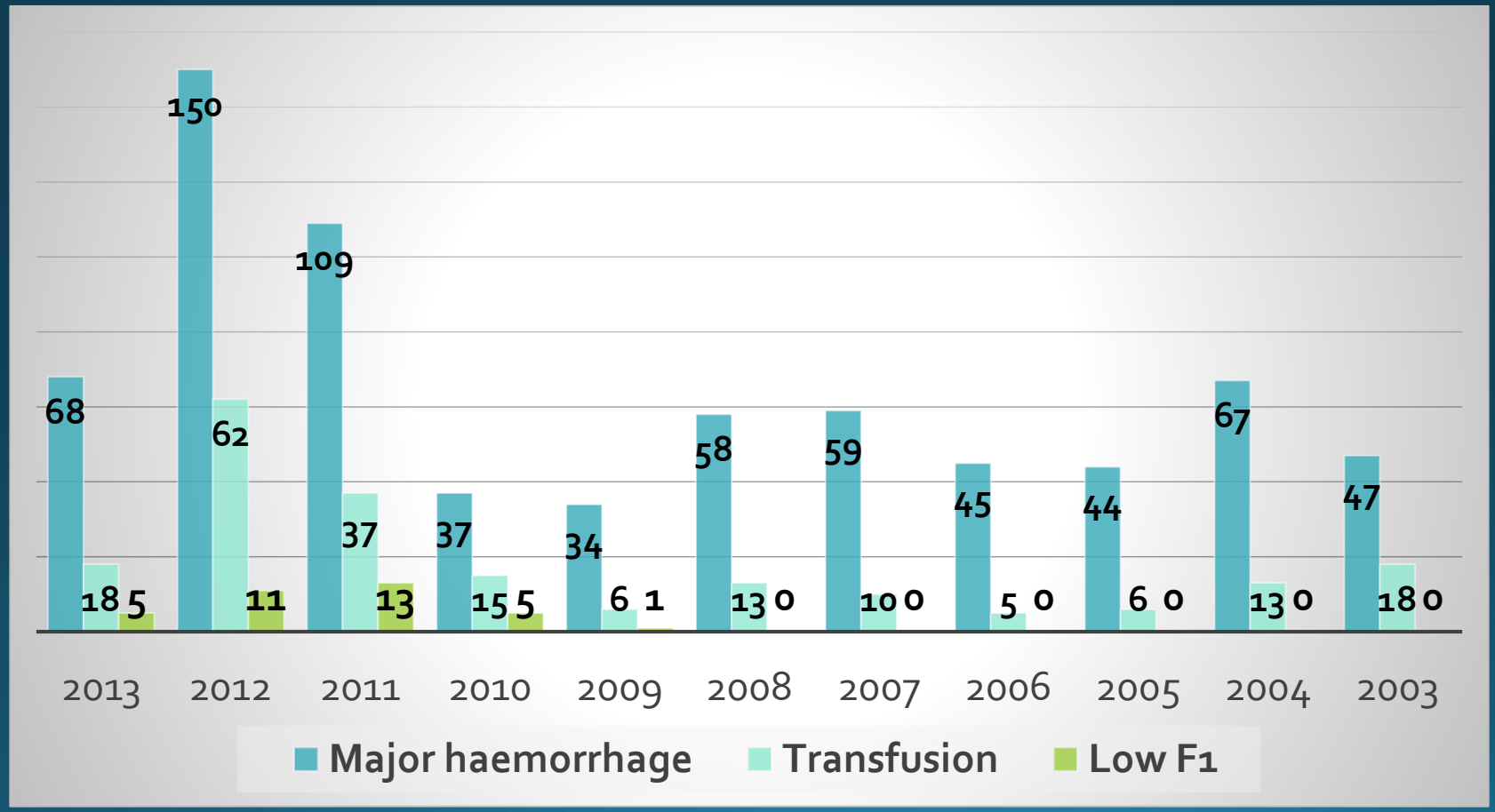
	Total pregnant population	<5 subpopulation	>5 subpopulation
Mean:	4,94 g/L	4,42 g/L	6,35 g/L
Range 95%:	3,51-7,38 g/L	3,43-4,96 g/L	5,11-8,48 g/L
SD:	1,00 g/L	0,42 g/L	0,72 g/L



Dilution experiment with a sample of 10 g/L fibrinogen level



The occurrence of hemorrhagic obstetric complication, transfusion, and low fibrinogen level between 2009 and 2013



Statistical obstetric indicators of cases above and under 5 g/L fibrinogen level

	F1≥5 G/L	F1<5 G/L	STATISTICAL ASSESSMENT
CASE NUMBER	509	1563	
MEAN AGE	30,84 years	30,75 years	p=0,704
MEAN GRAVIDITY	1,85	2,03	**p=0,01**
MEAN PARITY	1,46	1,63	**p=0,00002**
MEAN BIRTHWEIGHT	3365 g	3393 g	p=0,29
PREMATURE BIRTH FREQUENCY	23/509	65/1563	OR=1,09 (0,67-1,77)
CAESAREAN SECTION	200/509	548/1563	OR=1,2 (0,97-1,47)
GESTATIONAL DIABETES	18/509	35/1563	OR=1,6 (0,9-2,9)
PREECLAMPSIA	50/509	77/1563	**OR=2,1 (1,45-3,05)**

Risk reduction of major obstetric haemorrhage

- Definitions
- Epidemiology
- Causes
- Classification
- Diagnosis
- Treatment
- Prevention

- Early scan, regular US check
- Detailed history and risk assessment
- Folic acid and iron supplementation
- Continuing risk assessment
- Prophylactic measures (stop smoking and drug use, avoid prolonged labour, avoid hyperstimulation, G&S, Xmatch RBC, large-bore iv.cannula, prevention of atony, active management of 3rd stage, careful check of placenta, involve haematologist)
- **F1 screening**
- **F1 stock**
- **Preemptive F1-supplementation**

Thank you for your attention!

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