phn NORTH WESTERN MELBOURNE
An Australian Government Initiative

Shared Maternity Care Collaborative Workshop 2

Tuesday 15 October 2024

The content in this session is valid at date of presentation

Mercy Health
Care first

northern health
the northern way of caring

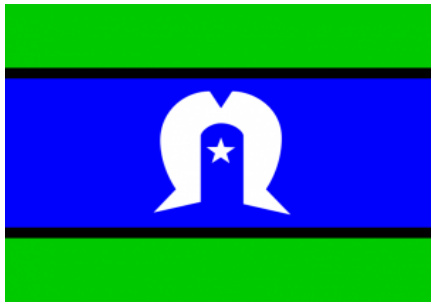
the women's
the royal women's hospital

Western Health

Acknowledgement of Country

The Royal Women's Hospital, Mercy Health, Northern Health, Western Health and North Western Melbourne Primary Health Network acknowledge the Traditional Custodians of the land on which our work takes place, The Wurundjeri Woi Wurrung People, The Boon Wurrung People and The Wathaurong People.

We pay respects to Elders past, present and emerging as well as pay respects to any Aboriginal and Torres Strait Islander people in the session with us today.



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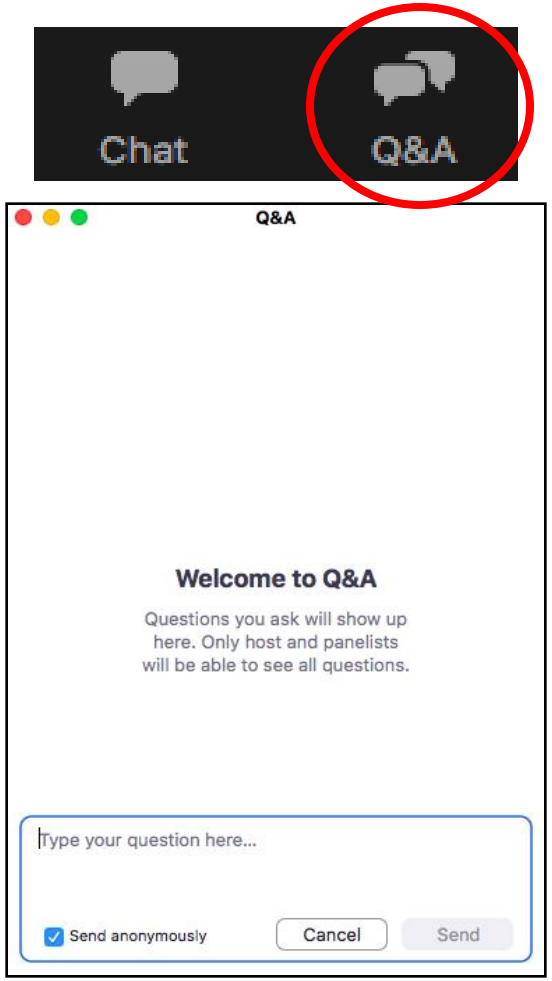

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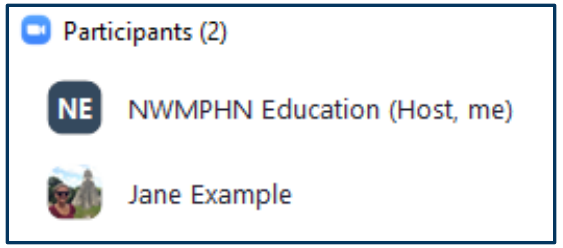

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Shared Maternity Care Collaborative

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Moderator

A/Prof Ines Rio – The Royal Women's Hospital

- A/Prof Ines Rio has extensive experience in many facets of health care and is committed to quality, effective, efficient, equitable and integrated health care services and the central importance and role of general practice and primary care in this provision.
- Ines is a GP, Head of the General Practice Liaison Unit and GP Obstetrician at the Royal Women's Hospital, Chief Medical Officer at Monash University
- Member of the:
    - Pharmaceutical Benefits Advisory Committee
    - TGA Advisory Committee on Vaccines
    - National Women's Health Advisory Council
    - CALD Communities Health Advisory Group
    - Australian Commission of Safety and Quality in Health Care

SMCC Workshop 2 Presentations

1. Gestational diabetes and thyroid disease in pregnancy, Dr Jessica Deitch
2. Haematological conditions in pregnancy, Dr Vanessa Manitta
3. Hospital and partner updates

Speaker

Western Health

Dr Jessica Deitch is an Endocrinologist at Western Health and Alfred Health and a PhD candidate with the University of Melbourne. Jessica graduated with MBBS(Hons) and BMedSc(Hons) from Monash University in 2015 and completed her endocrinology training through Alfred Health and Western Health with her FRACP awarded in 2023. Jessica has an interest in a broad range of areas within endocrinology, and a particular interest in obstetric endocrinology; her PhD and current research interests are related to screening and diagnosis of gestational diabetes.

Western Health

Shared Maternity Care Workshop

15th October 2024

Gestational diabetes and thyroid disease in pregnancy

Dr Jessica Deitch MBBS BMedSc(Hons) FRACP
Endocrinologist, Western Health
PhD Candidate, University of Melbourne

Overview

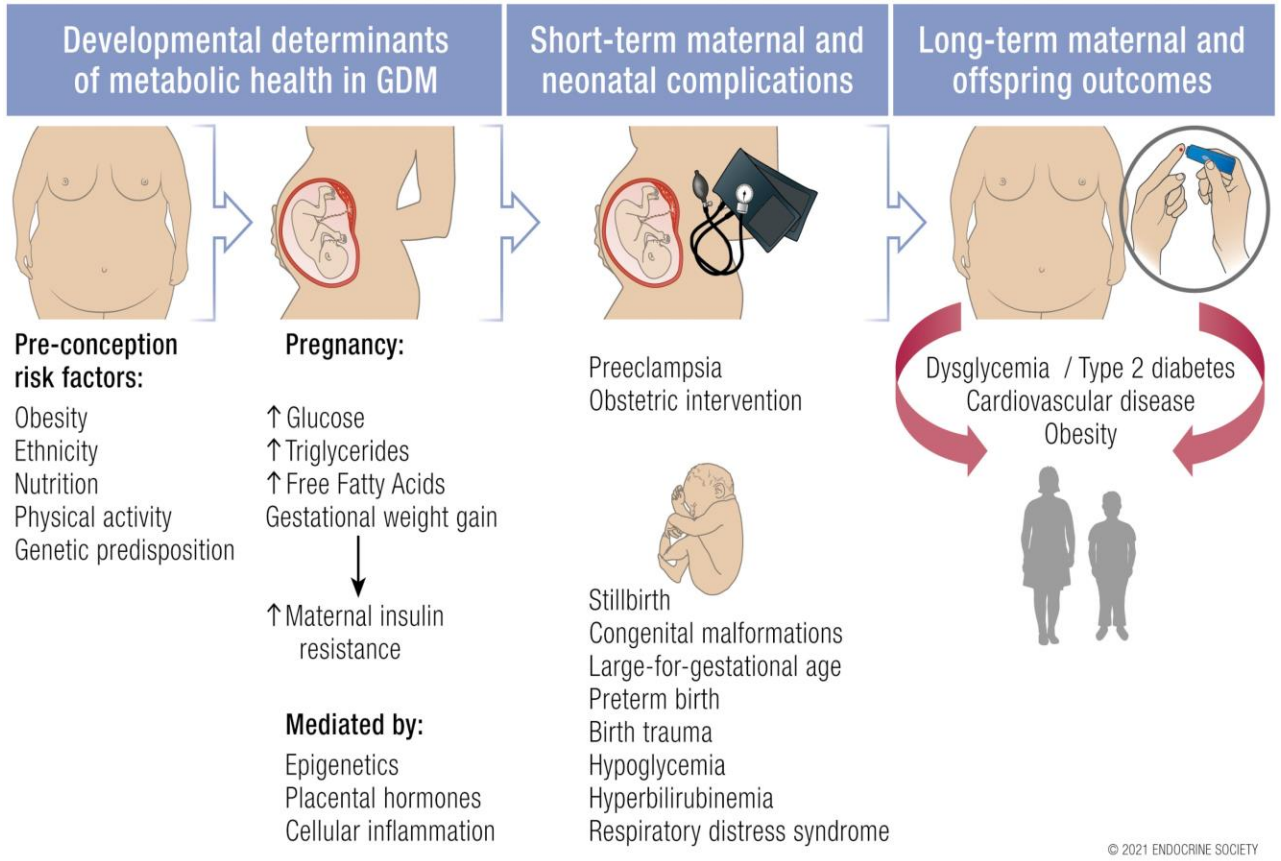
- Gestational diabetes mellitus
  - Significance
  - Current screening guidelines
  - Management
  - Long-term follow-up

- Thyroid disease in pregnancy
  - Thyroid hormone changes during pregnancy
  - Hypothyroidism and subclinical hypothyroidism
  - Hyperthyroidism in pregnancy
  - Postpartum thyroiditis

Western Health

Gestational diabetes mellitus

Gestational diabetes (GDM)

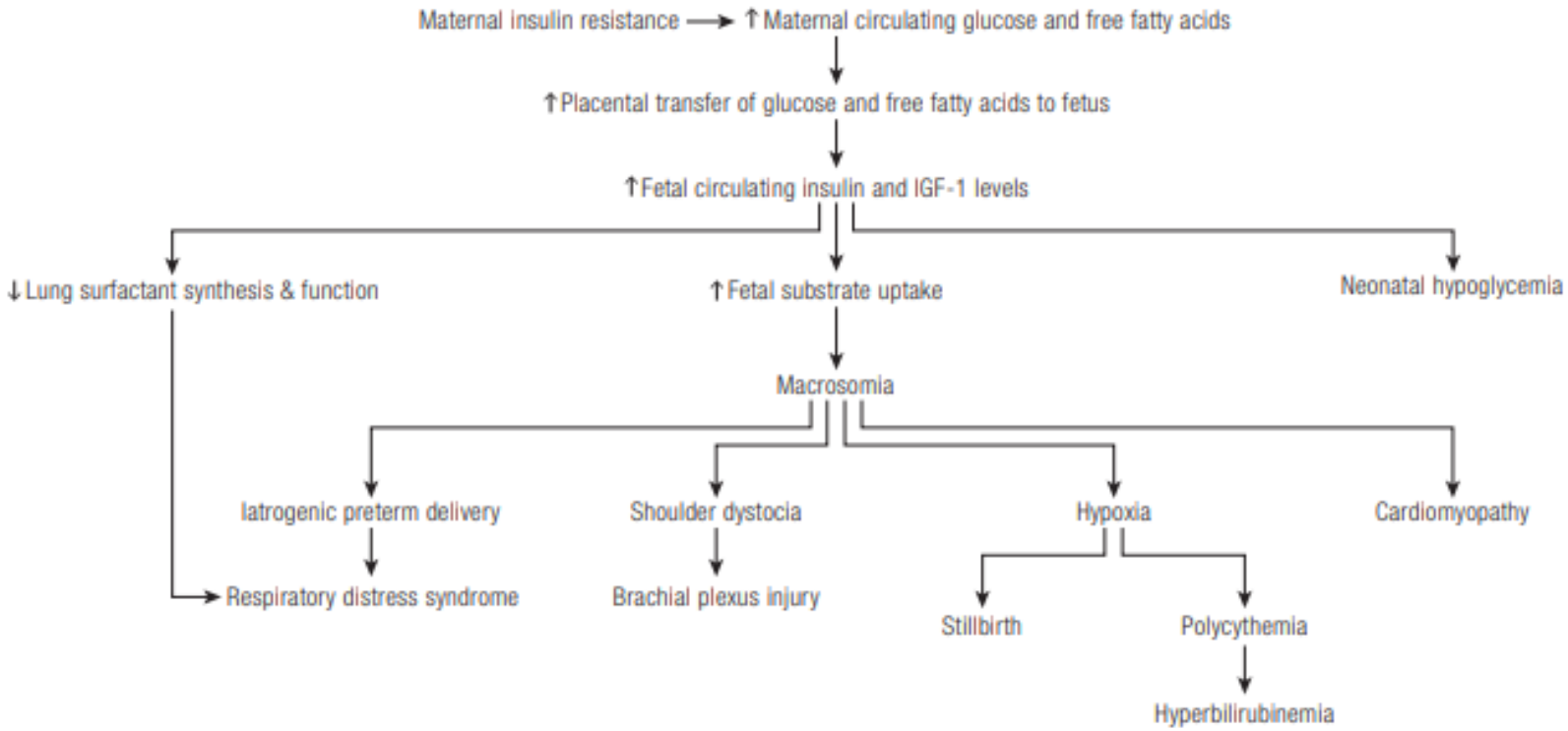


Abnormal glucose tolerance with onset during pregnancy

Pregnancy-related hormones (oestrogen, cortisol and human placental lactogen) cause insulin resistance which can result in GDM

Sweeting A, et al. Endocrine Reviews, 2022.

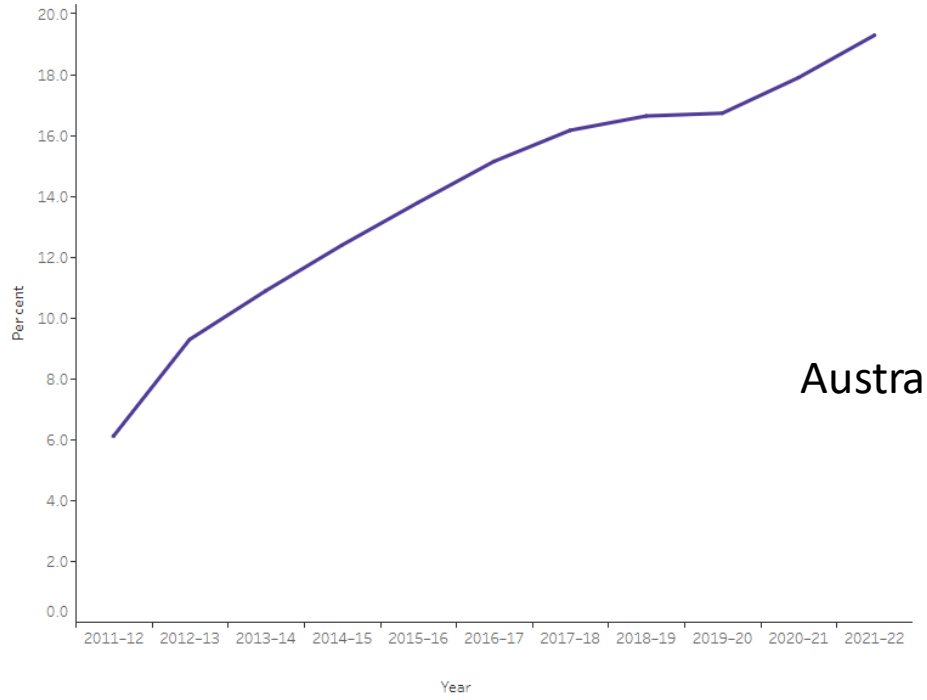
Perinatal complications



Sweeting et al, Endocrine Reviews 2022

GDM prevalence is increasing

Figure 2: Incidence of gestational diabetes, 2011–12 to 2021–22

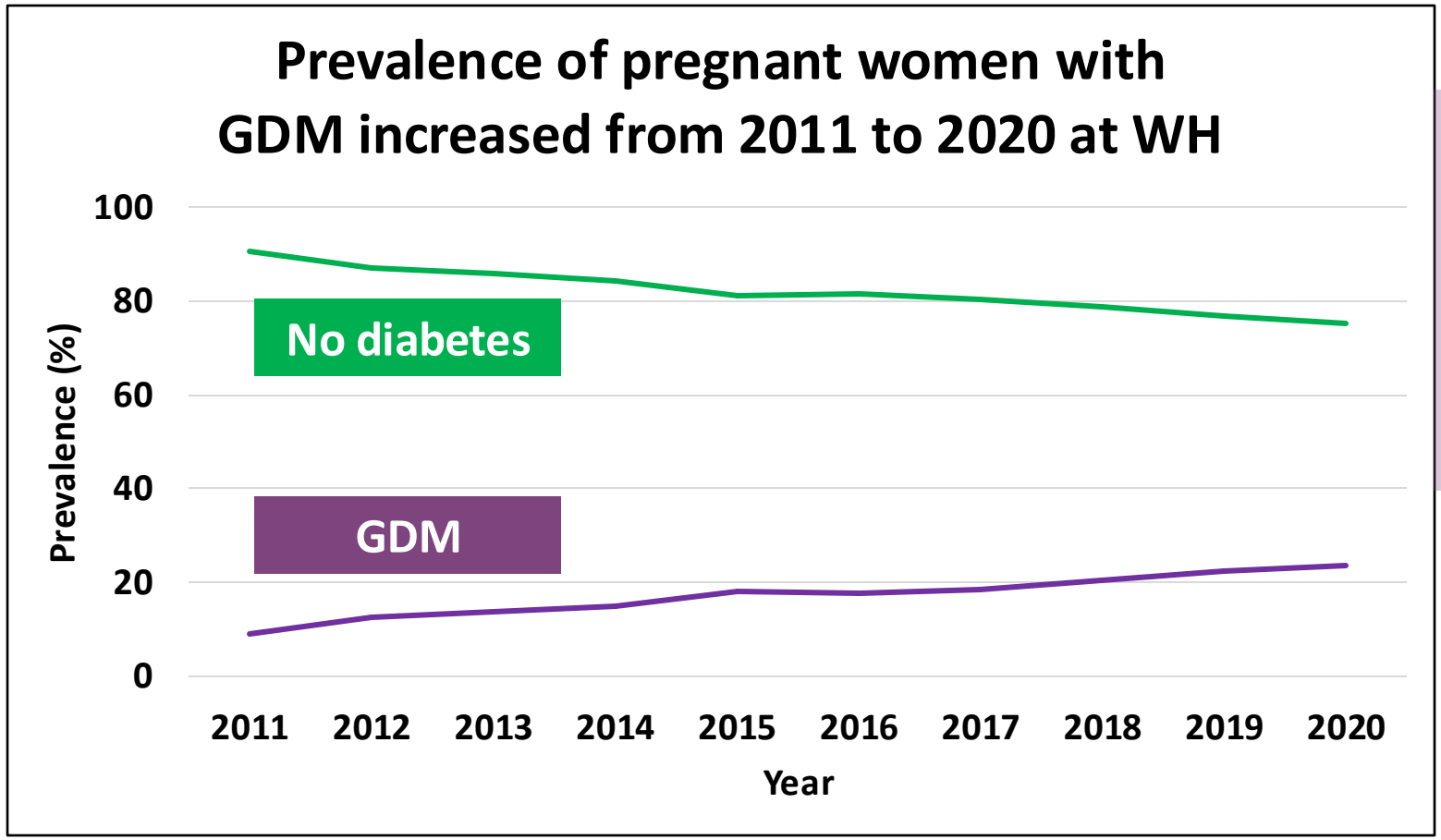


Australian GDM prevalence 2021-22 = 17.9%

- Epidemiological factors (background obesity rates, sedentary lifestyles, increasing age, growing proportion of higher risk ethnic groups in the population)
- GDM screening criteria change (2015)

Figure from Australian Institute of Health and Welfare, June 2024
Laurie GJ, et al. Int J Environ Res Public Health 2022.

Western Health GDM prevalence



GDM prevalence
2011: 8.9%
2020: 23.7%

Annual increase by 8.6%^ (95%CI 7.8, 9.4)

^Trend analysed by negative binomial regression

Figure adapted from Deitch J, et al. Diabetes Res Clin Prac, 2023.

GDM screening

- The optimal screening method remains controversial nationally and internationally

- Previous GDM diagnostic criteria focused on risk of future maternal diabetes
- Current diagnostic criteria has shifted towards identifying perinatal risk
- Lack of international consensus for GDM diagnosis and glucose treatment targets

Sweeting et al, Endocrine Reviews 2022

Table 1. Current international testing approach to gestational diabetes mellitus

Organization/ country	Selective vs universal testing	Method of screening	Screen positive threshold (mmol/L)	Diagnostic test	Diagnostic (plasma glucose) threshold for GDM (mmol/L)
IADPSG (30) WHO (11) ADIPS (33) FIGO (32) JDS (34) EBCOG (36) Endocrine Society (31) China (35)	Universal	One-step: 75-g 2-h OGTT		75-g 2-hour OGTT	Fasting ≥ 5.1 1-h ≥ 10.0 2-h ≥ 8.5 One abnormal value needed for diagnosis
ADA (41)	Universal	One-step: 75-g 2-h OGTT Two-step: 50-g GCT	≥7.2 to 7.8[a]	75-g 2-hour OGTT 100-g 3-hour OGTT	Fasting ≥ 5.1 1-h ≥ 10.0 2-h ≥ 8.5 One abnormal value needed for diagnosis Carpenter and Coustan[b] (17) or NDDG (13) Fasting ≥ 5.3 Fasting ≥ 5.8 1-hour ≥ 10.0 1-hour ≥ 10.6 2-hour ≥ 8.6 2-hour ≥ 9.2 3-hour ≥ 7.8 3-hour ≥ 8.0 Two abnormal values needed for diagnosis
ACOG[c] (19)	Universal	Two-step: 50-g GCT	≥7.2 to 7.8*	100-g OGTT	Carpenter and Coustan[b] (17) or NDDG (13) Fasting ≥ 5.3 Fasting ≥ 5.8 1-hour ≥ 10.0 1-hour ≥ 10.6 2-hour ≥ 8.6 2-hour ≥ 9.2 3-hour ≥ 7.8 3-hour ≥ 8.0 Two abnormal values needed for diagnosis[d]
CDA (42)	Universal	Two-step: 50-g GCT (preferred) One-step: 75-g 2-h OGTT (alternative)	≥7.8	50-g GCT 75-g 2-hour OGTT	≥11.1 mmol/L[e] Fasting ≥ 5.3 1-hour ≥ 10.6 2-hour ≥ 9.0 One abnormal value needed for diagnosis
NICE (38)	Selective	Risk factors[f]		75-g 2-hour OGTT	Fasting ≥ 7.0 2-hour ≥ 7.8 One abnormal value needed for diagnosis
CNGOF (39)	Selective[g]			First trimester fasting glucose 75-g OGTT[h]	≥5.1 Fasting ≥ 5.1 1-hour ≥ 10.0 2-hour ≥ 8.5 One abnormal value needed for diagnosis
DDG/DGGG (43)	Universal	Two-step: 50-g GCT One-step: 75-g OGTT (preferred)	≥7.5	50-g GCT 75-g OGTT	≥11.1 mmol/L[e] Fasting ≥ 5.1 1-hour ≥ 10.0 2-hour ≥ 8.5 One abnormal value needed for diagnosis
DIPSI (44)	Universal	One-step: 75-g OGTT		75-g OGTT	2-hour ≥ 7.8[i]

Sweeting et al, Endocrine Reviews 2022

GDM screening

Table 1 1991/1998 Australian Diabetes in Pregnancy Society (ADIPS) versus 2014 International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria for diagnosing gestational diabetes mellitus

	1991/1998 ADIPS		2014 IADPSG		2015 NICE	
	Type of test	**Positive criteria**	**Type of test**	**Positive criteria**	**Type of test**	**Positive criteria**
Screening test	50 g non-fasting glucose challenge test or 75 g non-fasting glucose challenge test	≥7.8 mmol/L ≥8.0 mmol/L	Nil	Not applicable (N)	Clinical risk assessment	Any one of five clinical risk factors[9]
Diagnostic test	75 g, 2 hours fasting glucose tolerance test (two levels)	Fasting ≥5.5 mmol/L 2 hours ≥8.0 mmol/L	75 g, 2 hours fasting glucose tolerance test (three levels)	Fasting ≥5.1 mmol/L 1 hour ≥10 mmol/L 2 hours ≥8.5 mmol/L	75 g, 2 hours fasting glucose tolerance test (two levels)	Fasting ≥5.6 mmol/L 2 hours ≥7.8 mmol/L

NICE, National Institute for Health and Care Excellence.

Cade TJ et al, BMJ Open 2019

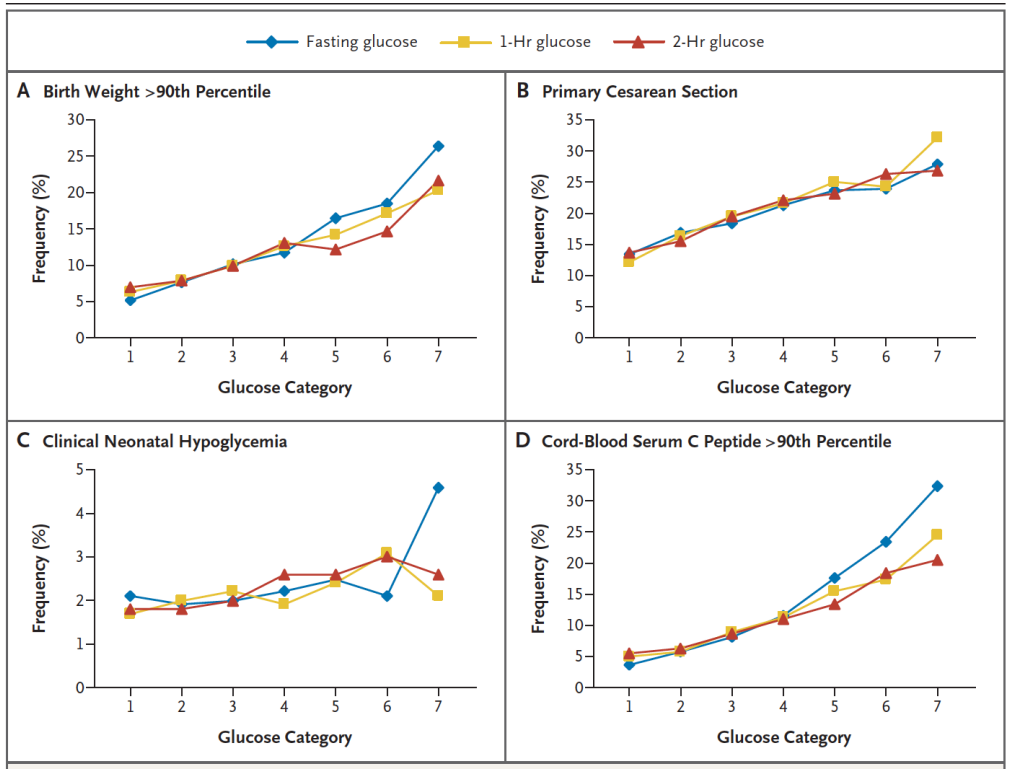
Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) Study

Western Health

- Large, international, multi-centre, prospective observational study
- Aim: to assess the risks of adverse pregnancy outcomes at various degrees of maternal glucose intolerance less severe than overt diabetes mellitus
- Evaluated relationship between glucose levels on the 75g 2 hour OGTT performed at 24 – 32/40 in over 25000 pregnant women with various neonatal outcomes
  - Neonatal primary outcomes (LGA, primary C/S, neonatal hypoglycaemia, cord blood serum C-peptide >90th centile) and secondary outcomes (pre-eclampsia, preterm delivery (<37/40), shoulder dystocia or birth injury, hyperbilirubinaemia, NICU admission
- Medical caregivers blinded to status of glucose tolerance except when predefined criteria were met (fasting glucose >5.8 and/or 2 hour glucose >11.1)

Metzger BE, et al. N Eng J Med 2008

Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study



- Results showed a continuous positive linear relationship between maternal fasting, 1-hr and 2-hr plasma glucose levels obtained on OGTT and risk of primary outcomes
- No specific glucose thresholds at which obstetric/ neonatal complications significantly increased

Metzger BE, et al. N Eng J Med 2008

Treatment of mild hyperglycaemia shown to reduce perinatal complications (1)

- Crowther CA, et al N Eng J Med 2005: Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS)
  - 1000 pregnant women between 24 – 34/40 with:
    - One or more risk factors for GDM on selective screening or a positive 50mg GCT (1 hour glucose ≥7.8mmol/L) AND
    - OGTT with fasting <7.8mmol/L and 2 hour 7.8-11.0mmol/L
  - Randomised to:
    - Routine care (no diabetes diagnosis) vs
    - Intervention group (treatment for GDM with target fasting <5.5mmol/L, 2 hour <7.0mmol/L)
  - Intervention group had lower risk of LGA/ macrosomia, increased rate IOL

Treatment of mild hyperglycaemia shown to reduce perinatal complications (2)

- Landon MB, et al N Eng J Med 2009: Maternal-Fetal Medicine Units Network (MFMU) trial
  - RCT with aim of determining whether treatment of women with mild GDM reduced perinatal/ obstetric complications
  - Inclusion criteria:
    - Pregnant women between 24 and 30+6/40 with glucose between 7.5 and 11.1mmol/L on GCT
    - Went on to have blind 100g 3 hour OGTT
    - Women with mild GDM enrolled, defined on blinded 100g 3 hour OGTT: fasting BGL <5.3 and two or three times BGL measurements that exceed thresholds (1 hour 10.0, 2 hour 8.6, 3 hour 7.8)
  - 485 women randomized to treatment group (treatment targets fasting glucose <5.3, 2 hour post meal <6.7)
  - 473 women randomized to routine care
    - If glucose checked on clinical concern, insulin commenced if fasting BGL 5.3 or random glucose 8.9
  - Results: treatment group had significant lower rates of: LGA, macrosomia, should dystocia, pre-eclampsia, gestational hypertension

Landon MB, et al. N Eng J Med 2009

International Association of Diabetes and Pregnancy Study Group (IADPSG) 2010

- IADPSG proposed new GDM diagnostic criteria
  - Highly influenced by HAPO study
  - Supported by RCTs – ACHOIS, MFMU
- **Consensus decision** to define diagnostic thresholds for fasting, 1-hr and 2hr glucose values for the 75g 2-hr OGTT based on the average glucose values at which the **odds of the primary outcomes were 1.75 times** the odds of these outcomes occurring at the mean glucose levels for the HAPO cohort
  - Only need one elevated glucose level for OGTT to make GDM diagnosis
    - Rationale as each glucose threshold represented broadly comparable level of risk in HAPO study

IADPSG Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010: 33(3):676-682

Australasian Diabetes In Pregnancy Society (ADIPS), 2014

Australasian Diabetes in Pregnancy Society (ADIPS) 2014 GDM screening guidelines

Selective screening in early pregnancy with 2-hr 75g OGTT

Universal 2-hr 75g OGTT at 24-28 weeks'

GDM diagnosed on OGTT with one of:

- Fasting glucose ≥5.1mmol/L
- 1-hr glucose ≥10.0mmol/L
- 2-hr glucose ≥8.5mmol/L

Nankervis A, et al. Australasian Diabetes in Pregnancy Society, 2014.

Early screening

Early OGTT if:
1 high risk
or
2 moderate risk factors

High risk factors

- Previous GDM
- Previous elevated glucose level
- Maternal age ≥40 years
- Family history DM (1st degree relative with diabetes or sister with GDM)
- BMI >35kg/m^2
- Previous macrosomia (baby with BW>4500g or >90th centile)
- PCOS
- Medications: corticosteroids, antipsychotics

Moderate risk factors

- Ethnicity:
  - Asian
  - Indian subcontinent
  - Aboriginal, Torres Strait Islander
  - Pacific Islander
  - Maori
  - Middle Eastern
  - Non-white African
- BMI 25 – 35kg/m^2

If normal early OGTT, still requires universal screening OGTT at 24 – 28 weeks' gestation

Nankervis A, et al. Australasian Diabetes in Pregnancy Society, 2014.

Early GDM

- Hyperglycaemia not meeting overt diabetes mellitus identified early in pregnancy (<20 weeks')
- Has been controversial
  - Significance of early GDM unclear
  - Risks/ benefits of treating or not treating unclear
- Observation data has shown women with early GDM have:
  - Accelerated fetal growth before 24 – 28 weeks' gestation
  - Greater perinatal mortality compared with women with GDM diagnosed at standard timing
  - A linear relationship between fasting glucose levels in early pregnancy and adverse pregnancy outcomes

Sovio et al Diabetes Care 2016, Immanuel et al Curr Diab Rep 2017, Bhavadharini et al Acta Diabetol 2022

Early GDM – TOBOGM trial

TOBOGM – Simmons et al NEJM 2023

- Multi-centre Australian RCT
- Women between 4 weeks' and 19 weeks 6 days' gestation who had risk factor for hyperglycaemia and diagnosis of GDM per IADPSG criteria randomised to receive immediate treatment for GDM or deferred until repeat OGTT 24-28 weeks' gestation
- Immediate treatment group had lower incidence of a composite of adverse neonatal outcomes (delivery <37/40, birth trauma, birth weight ≥4500g, neonatal resp distress, phototherapy, stillborn, neonatal death, shoulder dystocia) than no immediate treatment
  - This outcome driven by differences in respiratory distress
- No differences between groups observed for PIH or neonatal lean body mass
- 1/3 of women with GDM on early OGTT had normal OGTT at 24 – 28 weeks'
- Exploratory subgroup analyses suggest possible benefit of immediate treatment for women with a higher level glucose on OGTT and in those identified before 14 weeks' gestation
- Exploratory subgroup analyses suggest possible increased risk of SGA in those with lower level glucose on OGTT who received immediate treatment

GDM monitoring and targets

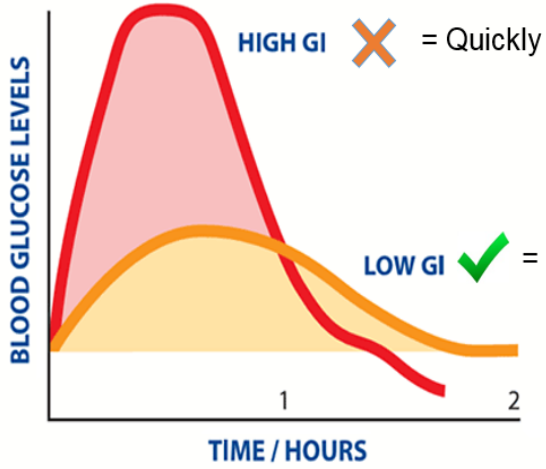
- BGL monitoring QID – fasting, 2 hours post meals
- Targets are centre-dependent:
  - Fasting <5.1 – 5.5mmol/L
  - 2 hour post prandial <6.5 – 6.7mmol/L

GDM management

- Nutrition:
  - Dietician review recommended – specific advice which differs from non-pregnancy and general pregnancy advice
  - Low GI diet with modified CHO intake
  - Aim to achieve normoglycaemia and provide the required nutrients for normal fetal growth within the recommend IOM gestational weight gain targets
  - Weight loss diets are not recommended during pregnancy but obese women can be advised to reduce energy input by up to 30% of usual
- Exercise:
  - Minimum of 30 minutes on most days of the week
  - Reduces insulin requirements
  - Improves insulin sensitivity

“LOW GI” carbohydrates

The **Glycaemic Index (GI)** is a measure of how quickly or slowly a carbohydrate food is digested and increases blood glucose levels.



HIGH GI ✗ = Quickly digested = Limit intake

✔ Aim to eat one low GI carbohydrate at every meal and snack.

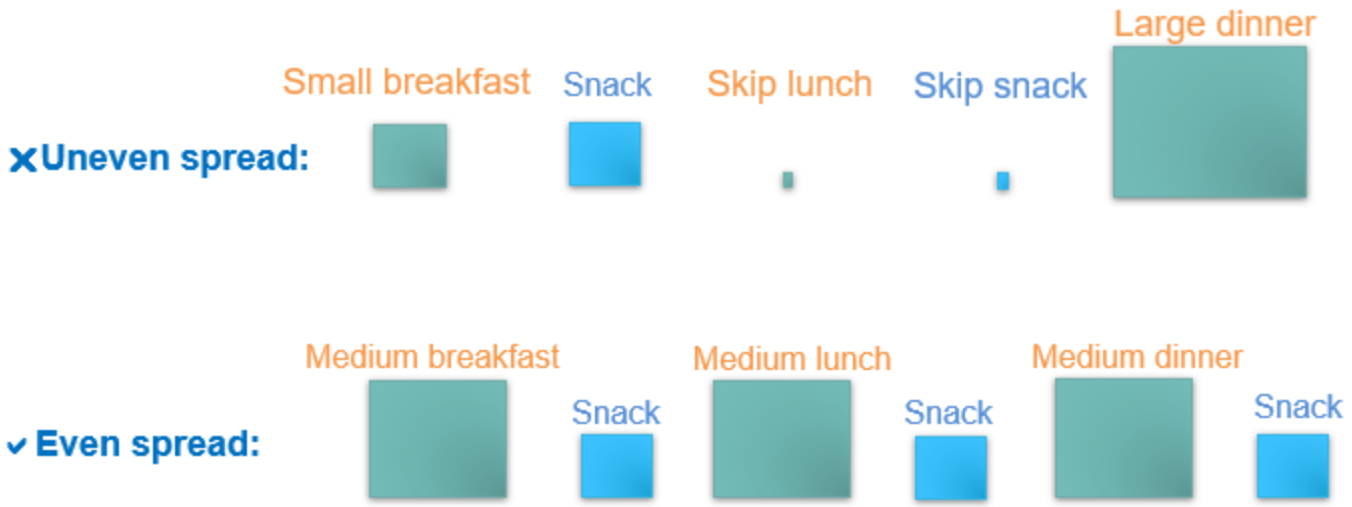
LOW GI ✓ = Slowly digested = Good choice

Use the tables below as a guide to making better carbohydrate choices.

Also visit this website (https://www.gisymbol.com/swap-it) for a “Swap It Tool” and look for the low GI symbol on food products:

Slide acknowledgement: Western health dietician Kim Davis

Carbohydrate amount and spread throughout the day is important



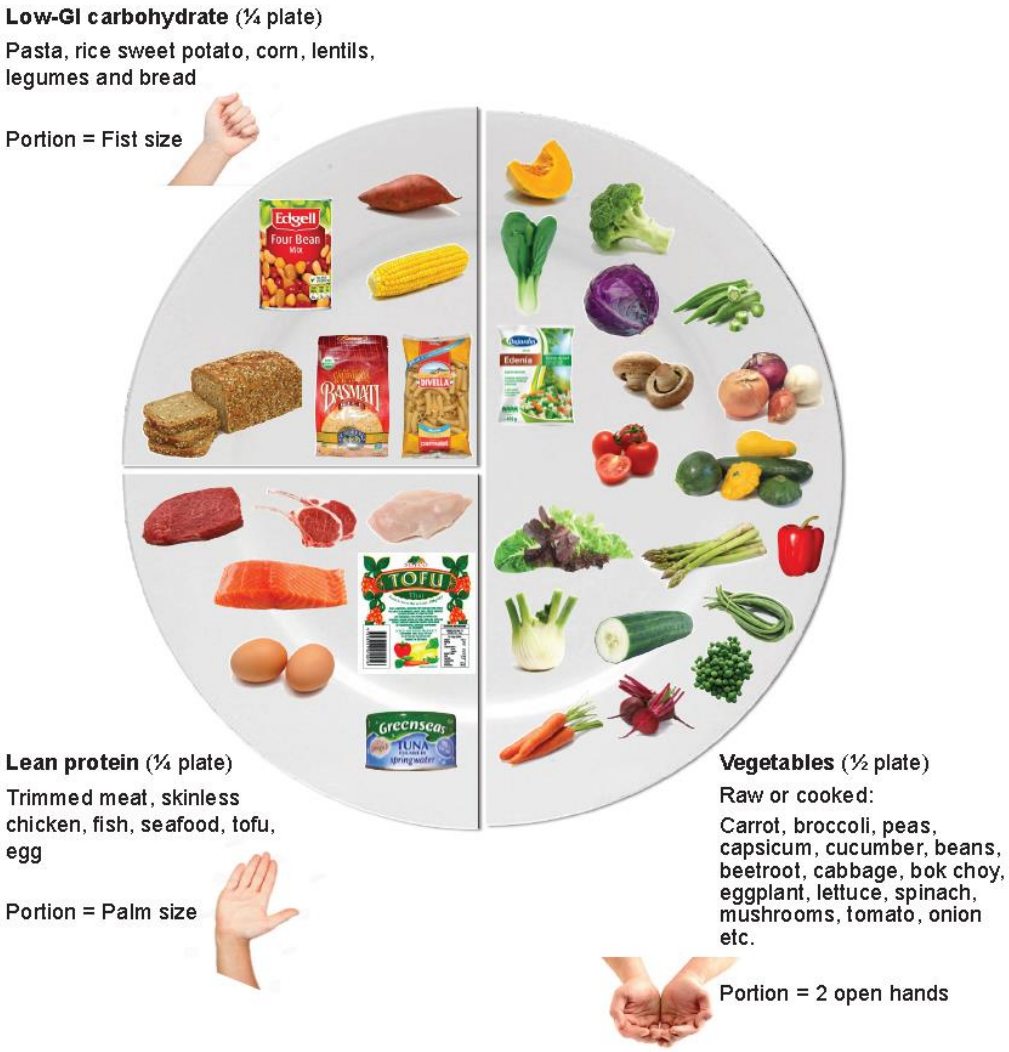
Slide acknowledgement: Western health dietician Kim Davis

Medium carbohydrate serves

At LUNCH or DINNER – choose one of the following carbohydrates:	
Pasta or noodles	Between 1 cup or 1 ¼ cups cooked
Rice (Basmati or Doongara)	Between 2/3 cup or 1 cup cooked
Sweet potato	3/4 cup cooked
Corn	Between ¾ or 1 cup corn kernals AND 1/4 cup sweet potato
Grainy bread	2 slices
Wholegrain tortilla or wrap	Between 1 to 1 ½ medium wrap
Wholemeal flat bread (Chapatti)	Between 1 ½ to 2 small chapatti
Wholemeal lebanese bread	Between ¾ to 1 lebanese bread
Quinoa	1 cup cooked
Lentils and legumes	1 cup cooked/canned AND 1/3 cup cooked rice

Slide acknowledgement: Western health dietician Kim Davis

Healthy Plate Model:



Source: Baker Institute

Slide acknowledgement: Western health dietician Kim Davis

Multi-cultural Diet and Vegetarian Diet

Diabetes Nutrition Information

Western Health

Multi-cultural plate model

50% Vegetables

× No creamy or oily sauces

× Does not include potato or pumpkin

✓Includes salad or cooked vegetables – aim for lots of colour.

2 CUPS

25% Protein

✓ Includes lean meat / chicken / fish (remove fat, skin, or breadcrumbs):

or Lentils or legumes (1 cup)
or 2 cooked eggs (not fried)
or cheese or paneer
or nuts
or tofu/soya chunks/soy nuggets/ textured vegetable protein

25% Carbohydrate

✓Choose low GI and wholegrain options:

- 1 cup cooked basmati rice with paneer or soya chunk curry dish.
- 1/2 cup cooked basmati rice with dhal or chickpea curry dish.
- 2 chappati/roti (thin, ~15cm diameter) with paneer or soya chunk curry dish.
- 1 ½ chappati/roti (thin, ~15cm diameter) with dhal or chickpea curry dish.
- 3 small idli
- 2 dosa
- ¾ cup cooked polenta or semolina
- 1 cup poha
- 1 large potato (~250g)
- 1 wholemeal Lebanese bread

How to make your chappati have a lower glycaemic index (GI):

✓ Use wholegrain atta flour and/or besan (chickpea flour) to make your chappati.

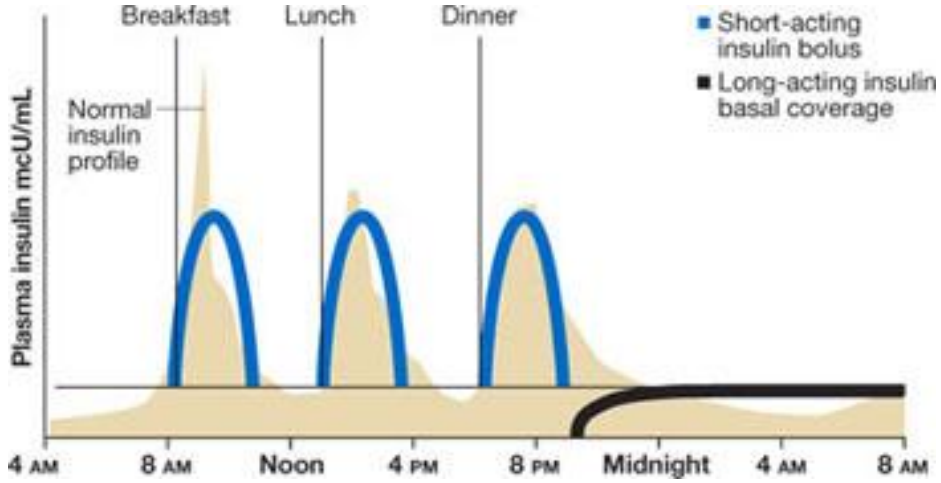
the women's
the royal women's hospital

Adapted from a resource prepared by the Royal Women's

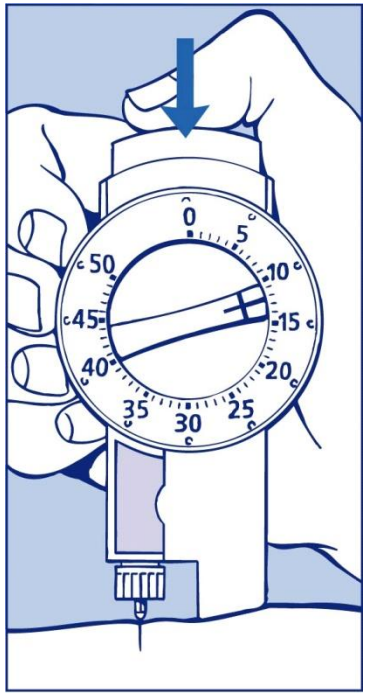
Slide acknowledgement: Western health dietician Kim Davis

GDM management: insulin

- Insulin is first-line therapy to manage hyperglycaemia if normoglycaemia not achieved with lifestyle intervention
- Regimens may vary centre to centre
- Basal bolus insulin regimen typically used at Western Health for GDM management:
  - Protaphane before bed (dosed based on fasting glucose)
  - Novorapid with meals (dosed based on 2-hour post prandial glucose)



Flexpen



Protaphane innolet

Insulin treatment practical tips

- What time is breakfast and evening meal?
  - Can dinner be eaten earlier? (e.g. before 8pm)
- Pre-bed snack
  - Elevated fasting glucose can reflect prolonged fasting (associated gluconeogenesis)
  - Can trial small supper
    - 10-15g low GI snack w protein (150ml milk with milo, hummus with veg sticks, Greek yoghurt w fruit) *or*
    - Protein only snack (handful of nuts, egg, high protein low CHO yoghurt)
- Eating overnight
- Shift work

GDM management: metformin

- Metformin does cross the placenta - No evidence of teratogenicity with extensive use
- Some concern re risk of SGA with metformin use - Area with ongoing research

Boggess et al JAMA 2023, Metformin plus insulin for preexisting diabetes or gestational diabetes in early pregnancy: the MOMPOD randomised clinical trial

- 794 participants randomised 1:1 to metformin or placebo with insulin for treatment preexisting diabetes or diabetes identified early in pregnancy; metformin commenced from enrollment (11 weeks - <23 weeks)
- Primary outcome: composite of neonatal complications (perinatal death, preterm birth, LGA/ SGA, hyperbilirubinaemia requiring phototherapy)
- No difference in primary composite outcome between groups therefore study halted at 75% accrual for futility in detecting significant difference in primary outcome
- Of individual components of the composite adverse neonatal outcome, metformin exposed neonates had lower odds of LGA when compared with placebo group, warranting further investigation

GDM management: metformin

Dunne et al JAMA 2023, Early Metformin in Gestational Diabetes: A randomized clinical trial

- 510 participants randomised 1:1 metformin to placebo
- Primary composite outcome: insulin initiation and fasting glucose ≥5.1mmol/L at week 32 or 38
- No difference in composite outcome between groups
- Metformin group had delayed time to insulin initiation, improved self-reported BGL level and lower GWG
- Metformin group has smaller neonates (lower mean birth weights, a lower proportion weighing >4kg, lower proportion in >90%centile, smaller crown-heel length) without differences in NICU/ other adverse neonatal outcomes

Post partum management

- Recommended for all women with GDM to have post partum OGTT 6 – 12 weeks
- Increased risk of developing T2DM (20 – 40% over 10 years)
  - Annual screening if high risk group, 1-2 years if lower risk group
  - Focus on prevention strategies for T2DM
- 30 – 50% risk of developing GDM in subsequent pregnancies
  - Ideally T2DM screening prior to conception
  - Early OGTT in pregnancy, repeat at 24 – 28 weeks if negative

Nankervis A, et al. Australasian Diabetes in Pregnancy Society, 2014.

Pre-gestational diabetes

Western Health

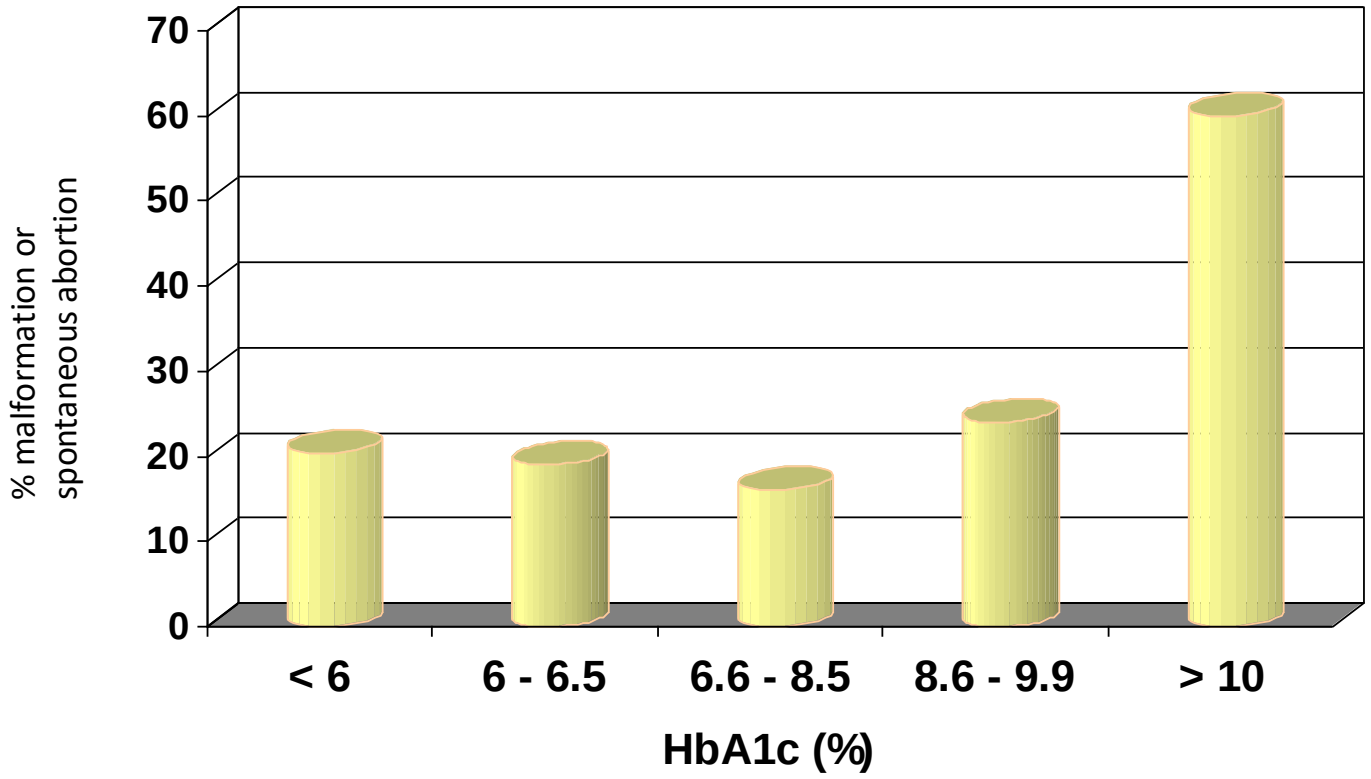
Pre-gestational diabetes – higher risk of significant adverse perinatal outcomes

Western Health

Maternal	Fetal
Increased insulin requirements	Congenital abnormalities 2-3x rate NTD/ cardiac defects
Hypoglycaemia	Macrosomia
Ketoacidosis	Preterm delivery
Miscarriage	Late stillbirth
Deterioration in retinopathy	Perinatal and neonatal mortality
Infection – UTI, resp, wound, endometrial, vaginal candidiasis	Neonatal hypoglycaemia
Proteinuria, oedema	Polycythaemia
Pre-eclampsia	Jaundice
Polyhydramnios	Respiratory distress syndrome
Increased risk of perinatal trauma	Diabetes
Increased C/S rate	Shoulder dystocia
	Fetal growth restriction

Modified from Handbook of Obstetric Medicine, Sixth Edition

Effect of poor glycaemic control on fetal outcomes



Greene et al Teratology 1989; 39:225

Pre-gestational diabetes and perinatal outcomes

Western Health

Murphy et al 2021, Lancet Diabetes Endocrinology

- 5-year national population-based cohort study of women with T1DM and T2DM across 172 maternity clinics in England, Wales and Isle of Man, UK
  - 17,375 pregnancy outcomes in 15,290 pregnancies
  - 8690 w T1DM, median maternal age 30 (10^{th}-90^{th} centile 22-37), median DM duration 13yrs (3-25)
  - 8685 w T2DM, median maternal age 34 (27-41), median DM duration 3yrs (0-10)
- Results:
  - Preterm delivery: T1 42.5% vs T2 23.4%, p<0.0001
  - LGA birthweight: T1 52.2% vs T2 26.2%, p<0.0001
  - Congenital anomaly: T1 44.8 per 1000 livebirths, terminations and fetal losses, T2 40.5 per 1000, p=0.17
  - Neonatal death: T1 7.4 per 1000 livebirths, T2 11.2 per 1000 livebirths
- Independent risk factors for perinatal death (stillborn/ neonatal death):
  - Third trimester HbA1C 6.5% or higher (OR 3.06, 95%CI 2.16-4.33 vs HbA1C <6.5%)
  - Being in the highest deprivation quintile (OR 2.29(1.16-4.52) vs lowest quintile)
  - Having T2DM (OR 1.65 (1.18-2.31) vs T1DM)
  - Across all HbA1C levels in third trimester, women with T2DM had higher rates of perinatal death compared with T1
  - Variations in HbA1C and LGA were associated with maternal characteristics (age, diabetes duration, deprivation, BMI)
  - In women with T2DM, only 18% on insulin and 22% taking 5mg folic acid pre pregnancy

Pre-gestational diabetes perinatal outcomes

- Importance of maternal glycaemia as modifiable risk factor for adverse perinatal outcomes
- Negative effect of maternal obesity in women with either T1 or T2
- Missed opportunities for pre-conception management of T2 highlighted – a concern that T2DM may be considered a less serious condition compared with T1

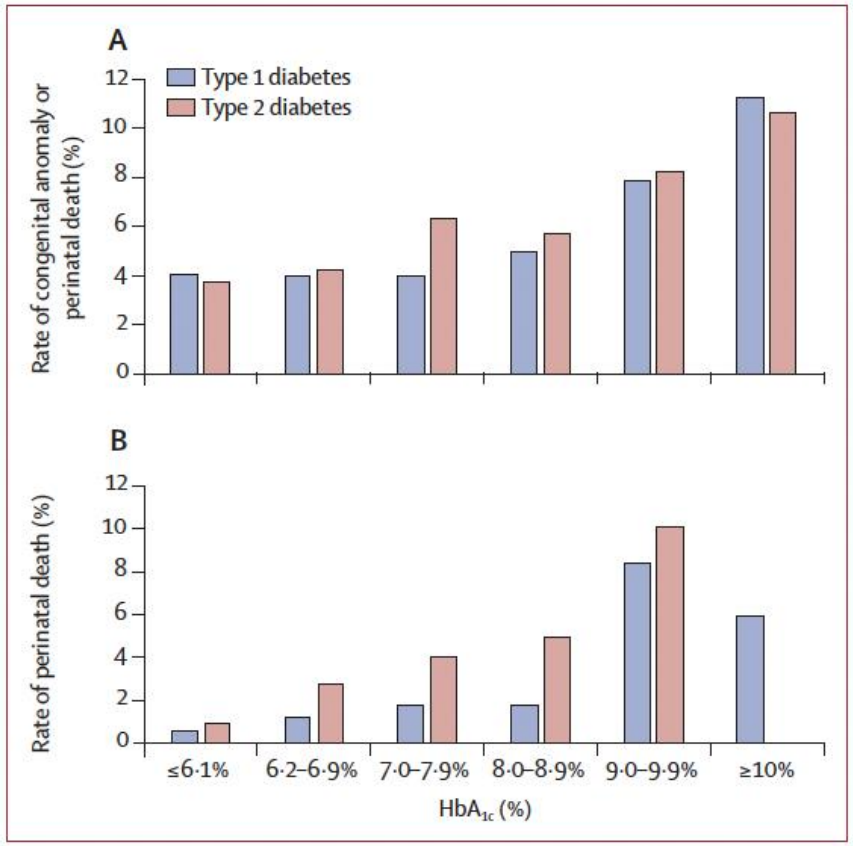


Figure 2: **Adverse pregnancy outcome by early (A) and late (B) maternal HbA_{1c} level, in pregnancies among women with type 1 or type 2 diabetes**
Rate of congenital anomaly or perinatal death (stillbirth and neonatal death) by first trimester HbA_{1c} level (A) and rate of perinatal death (stillbirth and neonatal death) by third trimester HbA_{1c} level (B). The HbA_{1c} categories are 6·1% (43 mmol/mol) or less, 6·2–6·9% (44–52 mmol/mol), 7·0–7·9% (53–63 mmol/mol), 8·0–8·9% (64–74 mmol/mol), 9·0–9·9% (75–85 mmol/mol), and 10% (86 mmol/mol) or higher.

Pre-gestational diabetes

- **Obesity, diabetes (particularly T2DM) and its complications are becoming *common* rather than rare in women of child-bearing age**
- Pre-conception counseling should be provided to all women of reproductive age with T1 or T2DM
- Appropriate contraception (consider counselling delaying pregnancy if HbA1C >8/8.5%)
- Glycaemic control – target HbA1C 6.5% (without significant hypoglycaemia)
- Assessment for diabetes-related micro and macrovascular complications
- Assessment for conditions associated with diabetes e.g. hypertension, obesity
- Medication review re pregnancy safety
- Folic acid 5mg daily – for at least 3 months prior to conception
- Women with T1DM – continuous glucose monitoring/ flash glucose monitoring subsidised through the National Diabetes Services Scheme (NDSS)

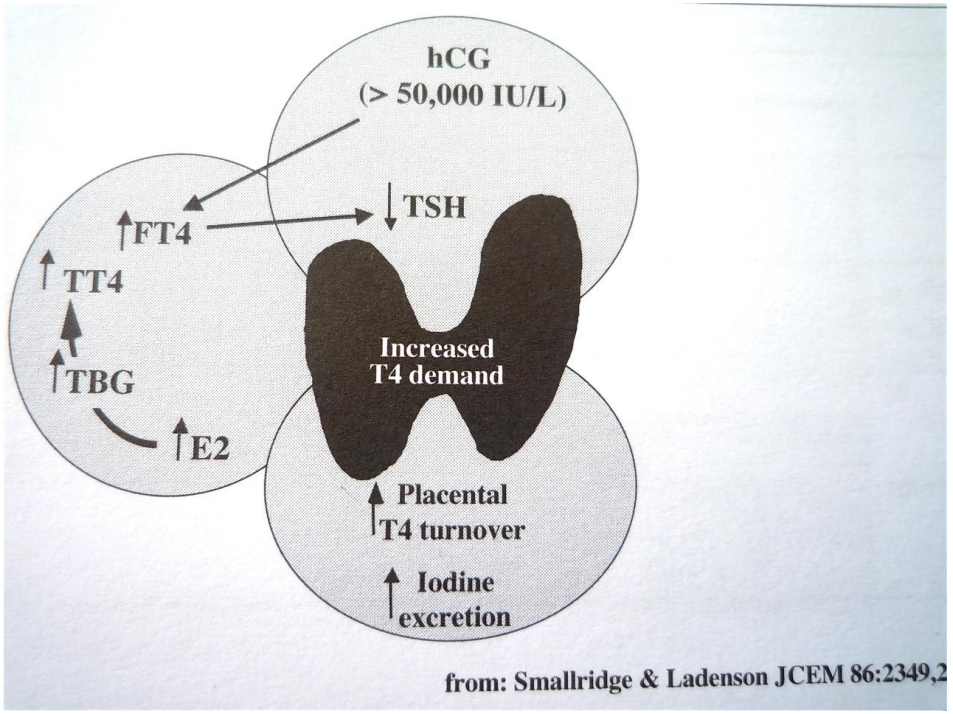
Western Health

Thyroid disease in pregnancy

Thyroid disease in pregnancy

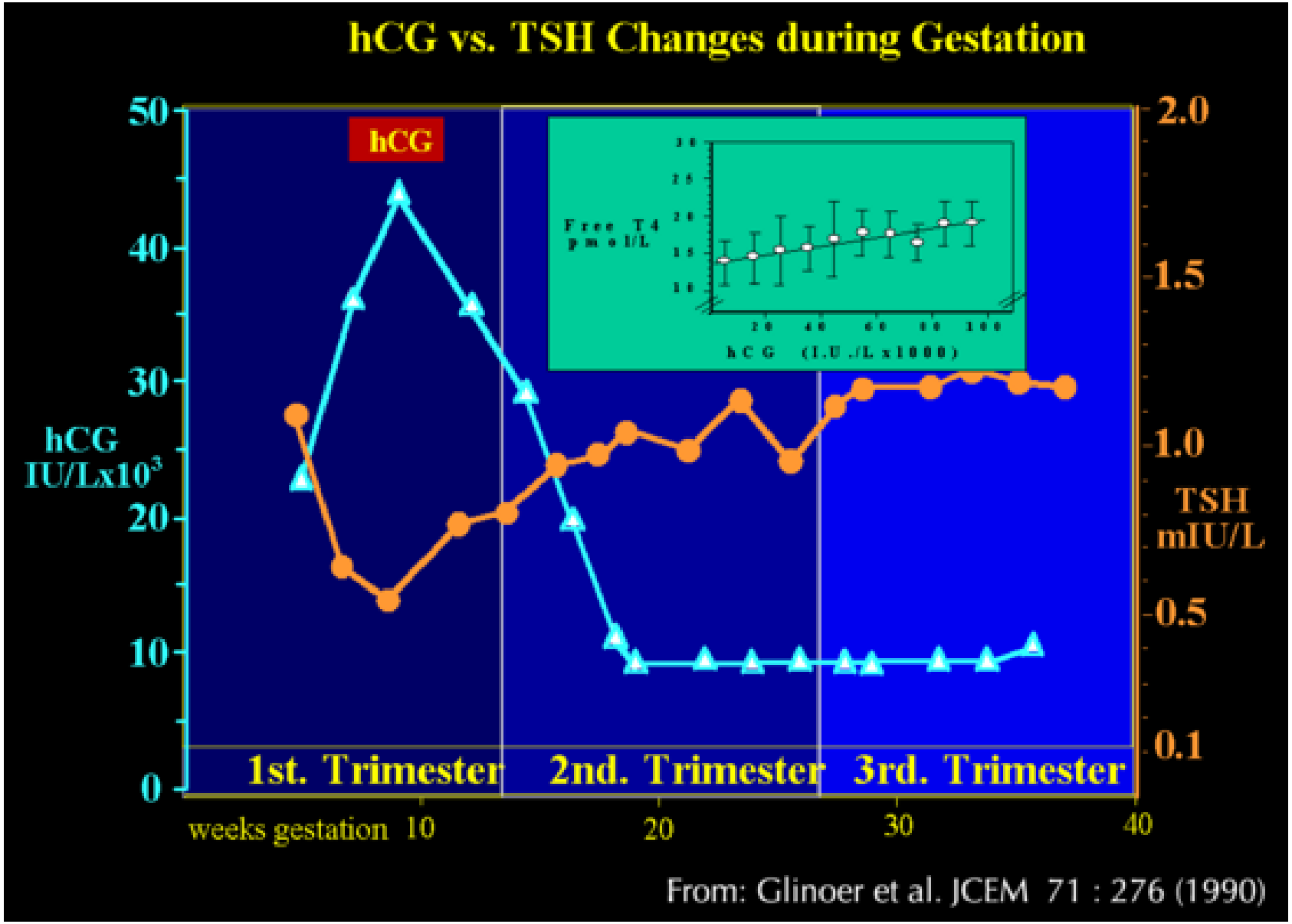
- Thyroid assessment in pregnancy
- Hypothyroidism
- Subclinical hypothyroidism
- Hyperthyroidism
- Postpartum thyroiditis

Thyroid function in pregnancy



Thyroid physiology changes occur to meet increased metabolic needs during pregnancy:

- Increase in thyroxine-binding globulin (TBG)
  - E2 -> increases in TBG production and decreases TBG clearance -> T4 and T3 production by gland increases to maintain adequate free thyroid hormone concentrations
- Stimulation of TSH receptor by hCG
  - hCG has similar structure to TSH and therefore has weak thyroid-stimulating activity
  - hCG increases soon after fertilization and peaks at 10 – 12 weeks

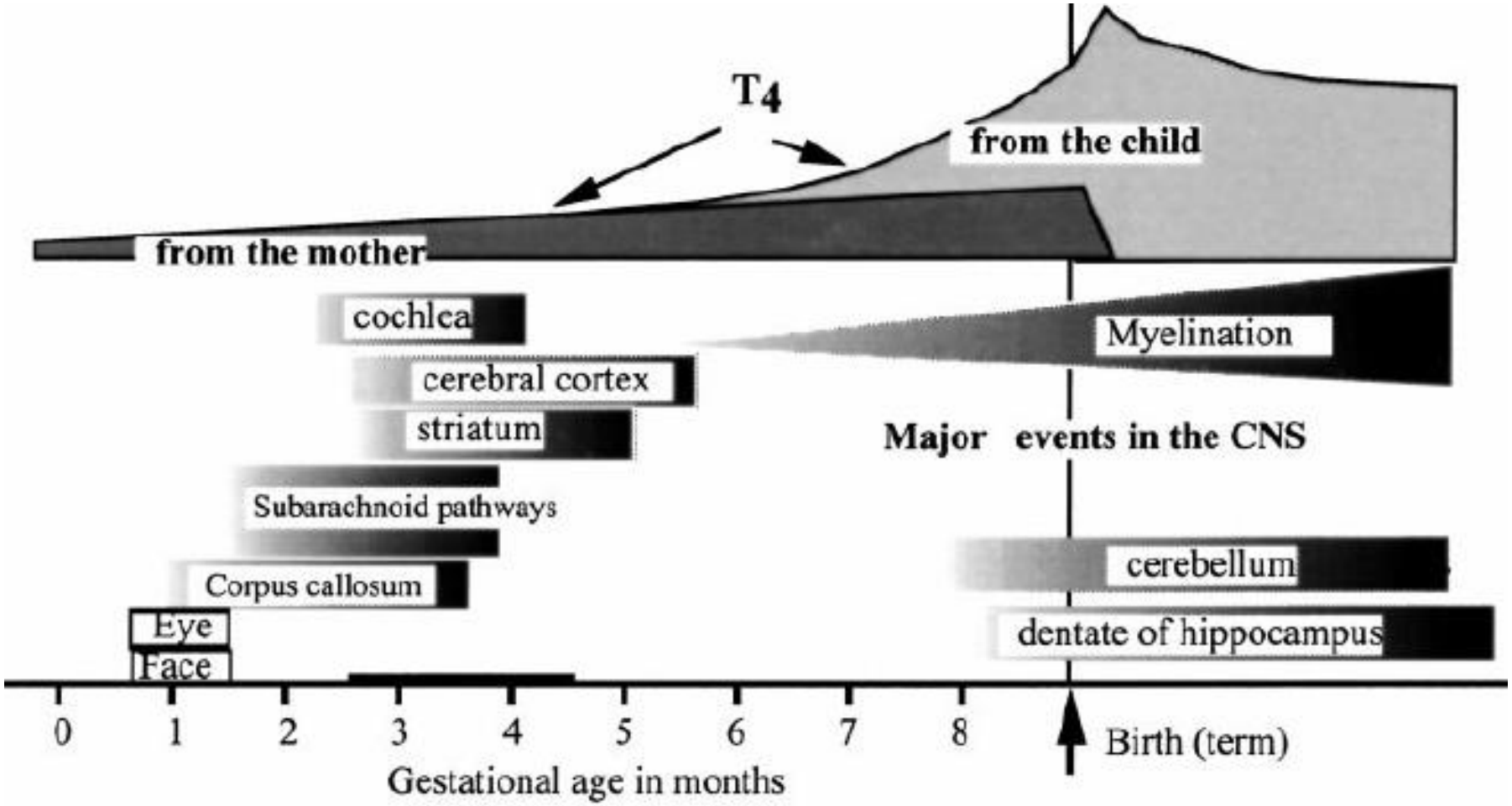


hCG-induced transient TSH suppression in 20% towards end of T1, of which 10% have increase fT4: gestational thyrotoxicosis, hyperemesis gravidarum

Largest decrease in TSH is seen in T1 (elevated hCG stimulating TSH receptor and increasing thyroid hormone production), after this serum TSH and reference range gradually rise in T2 and T3 but remain lower than nonpregnant women.

Fetal thyroid physiology

- Fetal thyroid begins secreting thyroid hormones at ~ Week 12
- Fetal TSH receptors become responsive to foetal TSH & TRAB (TSH receptor antibodies) at ~ Week 20
- Maternal FT4 crosses placenta in only minimal amounts (**small crucial amounts for foetal development**)
- TSH does not cross the placenta



Morreale de Escobar et al, JCEM 2000; 85: 3975

TSH variations during pregnancy

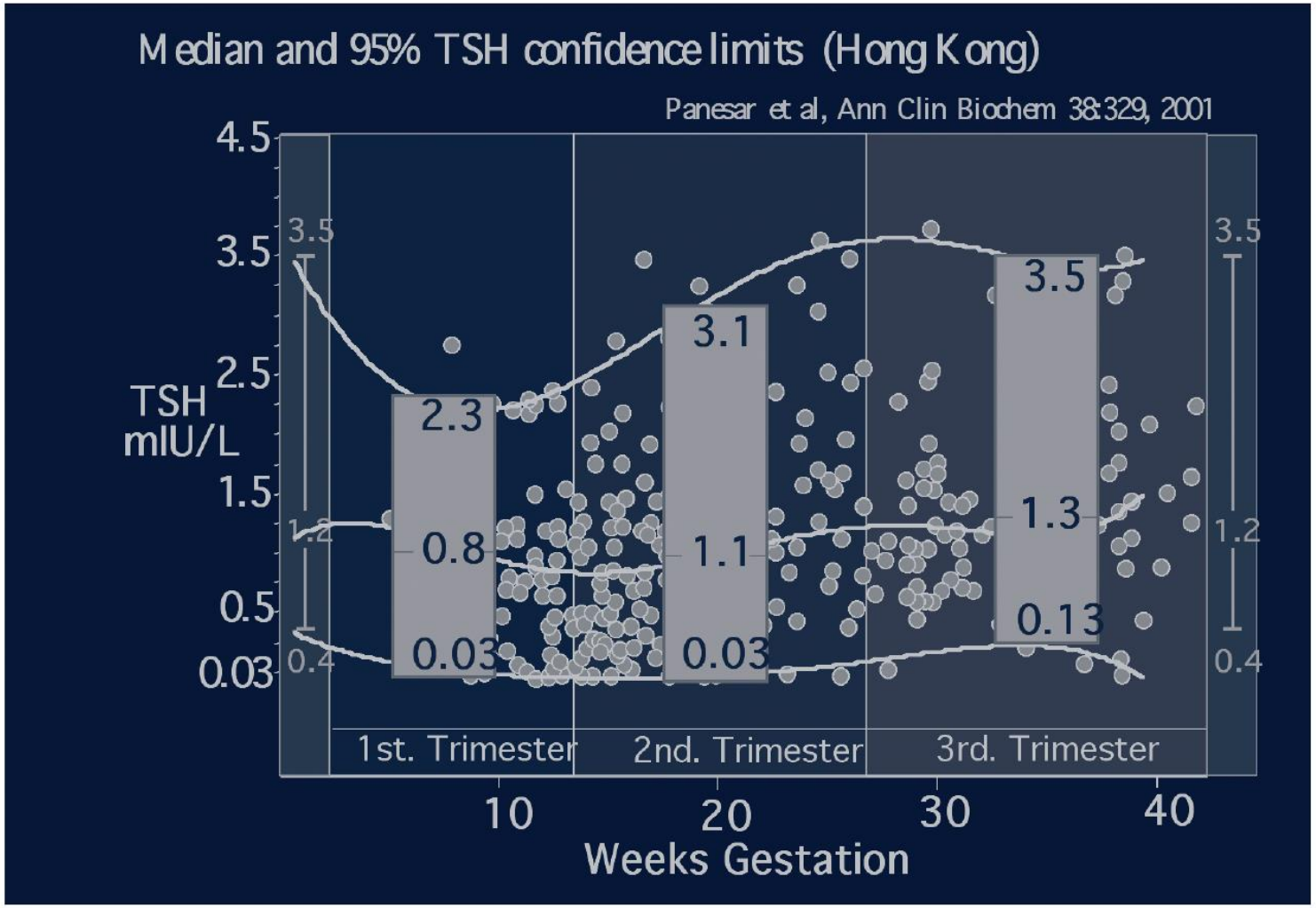


FIG. 1. Median and 95% confidence levels for TSH during pregnancy.

Important to note TSH variations are population specific – BMI, ethnicity, iodine intake

Pregnancy reference ranges for TFTs in Melbourne

- Very few local labs provide reference ranges for TFTs in pregnancy
  - Melbourne Pathology & Melbourne Health
    - TSH robust assay in pregnancy
    - Commercial FT4 assays affected by Alb & TBG levels – hence need for assay pregnancy specific ranges
- Roche Elecsys (E602) immunoassay (Melb. Path)

	TSH (mIU/L)	FT4 (pmol/L)	FT3 (pmol/L)
Non-pregnant female 18-49 years	0.5 – 5.0	11.0 – 21.0	3.1 – 6.0
1st Trimester	0.03 – 2.6	12.0 – 19.5	3.8 – 6.0
2nd Trimester	0.4 – 4.8	9.5 – 17.0	3.2 – 5.5
3rd Trimester	0.2 – 4.8	8.5 – 15.5	3.1 – 5.0

Assessment of thyroid disease in pregnancy

- **TFT screening is not routinely recommended during pregnancy**
- Screen for thyroid disease with a TSH if:
  - Symptoms of hypothyroidism/ hyperthyroidism
  - Personal history of thyroid disease
  - Personal history of head and neck irradiation/ prior thyroid surgery
  - T1DM/ other autoimmune condition
  - Recurrent miscarriage
  - Use of amiodarone/ lithium/ recent administration of high iodine load (e.g. iodinated radiocontrast agent)
- From 6/40, lab-specific TSH intervals should be used if available
  - If not available, TSH >4.0 is considered elevated

Hypothyroidism in pregnancy

Western Health

Overt and subclinical hypothyroidism

- Overt hypothyroidism:
  - TSH >2.5mU/L and decreased fT4
  - TSH >10mU/L, irrespective of fT4
- Subclinical hypothyroidism (SCH)
  - TSH 4 – 10mU/L, normal range fT4

- Isolated hypothyroxinaemia (normal TSH, low fT4)
  - Controversial whether this requires treatment – Melbourne Public Hospital consensus and American Thyroid Association recommend to not routinely treat

Alexander EK, et al. Thyroid 2017 27:3, 315-389
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Hypothyroidism in pregnancy

Causes of hypothyroidism
Autoimmune – Hashimoto's thyroiditis
Previous thyroidectomy – Nodular disease, Graves' disease, thyroid cancer
Previous radioactive iodine treatment – Toxic MNG, toxic adenoma, Graves' disease
Congenital hypothyroidism
Central/secondary hypothyroidism e.g. lymphocytic hypophysitis, panhypopituitarism (various causes)

Hypothyroidism in pregnancy – potential consequences

Western Health

- Challenging area to research
- Severe hypothyroidism associated with detrimental fetal consequences – cretinism due to iodine deficiency
- Association between untreated maternal hypothyroidism and reduction in IQ in offspring
  - Subsequent observational study of original study population demonstrated inverse correlation between severity of maternal hypothyroidism and IQ of 8-year old offspring
- Other reported potential perinatal complications – preterm birth, low birth weight, perinatal death, pregnancy-induced hypertension, pre-eclampsia, placental abruption, PPH

- **Overt hypothyroidism must be treated during pregnancy to reduce risk of potentially severe perinatal outcomes and adverse cognitive outcomes in offspring**
- Although untreated (or incompletely treated) hypothyroidism can adversely affect pregnancy, no data suggest that women with adequately treated hypothyroidism have an increased risk of any obstetric complication. Therefore, there is no indication for any additional obstetric testing or surveillance in pregnancies of women with hypothyroidism who are being monitored and treated appropriately.

Hetzel BS, MJA 2006;185:646-50; Haddow et al, N Eng J Med 341:549-555, 1999
Klein RZ et al, J Med Screen 2001;8:18-20; Pop et al. Clin Endocrinol, 2003: 59:282-288

Hypothyroidism in pregnancy – management

- Pre-conception target TSH <2.5mU/L
  - Caution in secondary hypothyroidism – TSH cannot be used for treatment target
- Increase usual dose of thyroxine by 25-30% as soon as pregnancy confirmed
  - Patient education to self increase
- During pregnancy check TFTs 4-6 weekly to ensure at target (TSH <2.5mU/L)

- If overt hypothyroidism diagnosed in pregnancy:
  - Early endocrinology input – particularly for significantly abnormal TFTs
  - Rapid correction of hypothyroidism required
  - Likely to need much higher doses than non-pregnant women

Hetzel BS, MJA 2006;185:646-50; Haddow et al, N Eng J Med 341:549-555, 1999
Klein RZ et al, J Med Screen 2001;8:18-20; Pop et al. Clin Endocrinol, 2003: 59:282-288

Hypothyroidism in pregnancy – management post partum

- Pre-existing hypothyroidism
  - Return to pre-pregnancy dose
- Newly diagnosed hypothyroidism during pregnancy
  - Dose appropriate for weight
  - Probably need reduction in thyroxine dose from delivery dose

- TFTs 6 weeks post partum to ensure adequate replacement
- Frequency of monitoring post this dependent on TFT stability
  - Aim to keep TSH ≤2.5mU/L with future pregnancy planning

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Subclinical hypothyroidism during pregnancy: the Melbourne public hospitals consensus

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Key words
subclinical hypothyroidism, hypothyroidism, pregnancy.

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Abstract

Background: Interest in potential adverse outcomes associated with maternal subclinical hypothyroidism (normal free T4, elevated thyroid-stimulating hormone (TSH)) has increased significantly over recent years. In turn, the frequency of maternal thyroid function testing has risen, despite universal thyroid function screening not being recommended, leading to a marked increase in referrals to obstetric endocrinology clinics. In 2017 the American Thyroid Association revised their diagnostic and management guidelines. Although welcome, these new guidelines contain recommendations that may cause confusion in clinical practice.

Aim: To ensure uniform practice in the diagnosis and management of subclinical hypothyroidism in pregnancy across all Melbourne public hospitals.

Subclinical hypothyroidism (SCH)

- 2-3% of pregnancies
- Pregnancy brings out diminished thyroid reserve
- TSH above trimester specific reference range with normal fT4/fT3
  - TSH targets if assay does not have trimester specific range is same as overt hypothyroidism

- Possibility that SCH may cause long-term effects on fetal brain development is contentious
- Link between SCH and adverse pregnancy outcomes also unclear
- Not proven to modify long term neurological development in offspring
- Studies are mainly in antibody positive women
- One of the most accepted associations is between SCH and miscarriage, however even here the study findings are contentious.
- No clear evidence that anti-thyroid antibody positive women with TSH<4mU/L are at increased risk of miscarriage

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The Melbourne Public Hospitals Consensus

- **Consensus based – poor evidence**

- **Thyroxine therapy started if TSH >4mU/L**
  - Where population/gestation specific TSH reference intervals are available, use TSH results > ULN of ref intervals instead of TSH >4mU/L
- Anti TPO Ab checked in all pregnant women with TSH >4mU/L
- Isolated hypothyroxinaemia (low fT4, normal TSH) not routinely treated
- When starting thyroxine, typically start 50mcg daily
- **Target TSH on treatment with thyroxine: 0.1 – 2.5 mU/L**
- Recheck TFTs 6 weekly after thyroxine initiation and 6 weekly throughout pregnancy to guide thyroxine dose
  - If TSH is in target range at 30 weeks' gestation, further TFTs are not required for rest of pregnancy

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The Melbourne Public Hospitals Consensus

- Thyroxine is ceased after delivery except those
  - (1) Contemplating repeat pregnancy within 12 months of giving birth
  - (2) Attempting to conceive again with history of unexplained spontaneous miscarriage
  - (3) TSH >10 mU/L prior to commencing thyroxine therapy
  - (4) Strongly positive anti-TPO antibodies (> 3x ULN) – risk of development of overt hypothyroidism
- When thyroxine is continued, thyroxine cessation should be considered on an annual basis (unless TSH was >10 mU/L)
- All women should have TSH/ FT4 rechecked 6 weeks postpartum

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Hyperthyroidism in pregnancy

Western Health

Hyperthyroidism in pregnancy

Causes of hyperthyroidism in pregnancy
Gestational transient hyperthyroidism (bHCG induced) (1 - 3% of pregnancies)
Graves' disease (0.4 -1% of women pre-pregnancy, 0.2% during pregnancy)
Toxic thyroid adenoma
Toxic multinodular goitre
Thyroiditis
Excessive ingestion of thyroxine
Molar pregnancy
Choriocarcinoma

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Hyperthyroidism in pregnancy

Distinguishing Graves' disease from gestational hyperthyroidism can be challenging

	Graves' disease	Gestational hyperthyroidism
Goitre/ orbitopathy	Yes (not always present)	No
TSHrAb positive	Yes	No
TPO & Tg Ab	Yes/No	Yes/No
Bruit	Yes (not always present)	No
FT4 levels	+++	++
Morning sickness	Yes/No	Yes, often debilitating

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Gestational hyperthyroidism

Gestational hyperemesis & hyperthyroidism; gestational thyrotoxicosis; gestational hyperthyroidism; b-HCG induced hyperthyroidism

- 0.5 – 10 cases per 1000 pregnancies
- B-HCG or molecular variant proteins related to B-hCG bind to TSH receptors on maternal thyroid -> displaces maternal TSH. Binding affinity of B-hCG is significantly less than maternal TSH but extremely high B-hCG levels overcome maternal TSH.
- Often associated with hyperemesis gravidarum
- Other conditions associated with hCG-induced thyrotoxicosis include multiple gestation, hydatiform mole, choriocarcinoma

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Gestational hyperthyroidism

- Measure TSH, FT4, FT3 and TRAB
  - Suppressed TSH and elevated FT4/ FT3 levels
- Can be difficult to differentiate from Graves' disease
  - Can occur in women with Graves' disease
  - In general:
    - T3 tends to be disproportionately elevated more than T4 in thyrotoxicosis caused by direct thyroid hyperactivity
    - T4 tends to be disproportionately elevated more than T3 in thyrotoxicosis caused by destructive processes such as thyroiditis
- TFT abnormalities can be significant, but are usually limited to first half of pregnancy
  - Notably as hyperemesis settles, there is a parallel improvement in TFT abnormalities – majority of cases TFTs normalise by late half of pregnancy

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Gestational hyperthyroidism

Management

- Supportive therapy – management of dehydration and hospitalisation if needed
- Anti thyroid drugs not recommended
  - May be used by endocrinology in severe cases where Graves' is suspected and antibody testing is pending
- Beta-blockers may be considered

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Graves' disease in pregnancy

- Important condition in pregnancy and post-partum - not being covered in detail today

- Various presentations in pregnancy:
  - New diagnosis in pregnancy
  - Pre-existing Graves'
  - Women on ATD at time of conception
  - Women in remission and then relapse of Graves' during pregnancy or in postpartum period
  - Post I-131 or thyroidectomy and is taking thyroxine replacement but positive TSHrAb (approx. 30%)

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Graves' disease in pregnancy

- Pre-conception counselling **very** important – advise contraception in uncontrolled Graves'
- Obstetric and medical complications related to control of maternal hyperthyroidism and duration of euthyroid state throughout pregnancy – poor control associated with pregnancy loss, pregnancy-induced hypertension, prematurity, low birth weight, IUGR, stillbirth, thyroid storm, maternal CCF
- Graves' disease activity fluctuates in pregnancy/post-partum
  - Exacerbation in first trimester (high levels of hCG), improvement in late gestation
  - Often post-partum exacerbation (up to 18 months of delivery)
- Women needing ATD in pregnancy – balance of thyrotoxicosis risk on mum/baby with risk of possible teratogenic side effects of ATDs
  - Use smallest possible dose and cease where possible
  - Aim to keep FT4 levels at or just above non-pregnancy reference range
  - PTU in first trimester and then carbimazole second and third trimester
- If thyroidectomy required for management, should be performed during second trimester

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Graves' disease in pregnancy

- TSHrAb testing must be done during pregnancy:
  - Simulating, binding and inhibitory varieties of TSHrAb freely cross placenta and can stimulate fetal thyroid gland (-> fetal hyperthyroidism/ neonatal Graves' disease)
  - Measure if: current Graves', history of Graves' who are in clinical remission (even if on thyroxine), previous neonate with neonatal Graves', previous TSHrAb positivity
  - Measure by 22/40 and again if third trimester if positive
- TSHrAb positive women +/- requiring ATD during pregnancy:
  - Specialised management issues – influenced by placental transfer of Ab, ATD, maternal thyroxine but no placental transfer of TSH
  - Maternal TFT monitoring in addition to fetal anatomy ultrasound and repeated scans as clinically indicated

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Subclinical hyperthyroidism

- Low TSH, normal fT4/fT3
- No evidence of harm to mother or fetus
- Numerous pregnancies in 1st trimester will show this pattern of TFTs (as discussed earlier in presentation)
  - Physiological in vast majority of pregnancies

Management:

- Don't treat with anti-thyroid drugs
- Examine thyroid for nodular changes – if thyroid nodule clinically evident, confirm with ultrasound and refer to endocrine
- No nodular changes, repeat TFTs in approx. 6 weeks – likely that subclinical hyperthyroidism will resolve as pregnancy progresses
- If continues throughout pregnancy:
  - If hyperemesis still, TFTs likely to normal post partum
  - If no hyperemesis/ cause for low TSH, endo referral for further work-up

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Post partum thyroiditis

Western Health

Post partum thyroiditis (PPT)

- Thyroid dysfunction (excluding Graves') in the first postpartum year in women who were euthyroid prior to pregnancy
- Inflammatory autoimmune condition
- Classically, transient thyrotoxicosis followed by transient hypothyroidism and return to euthyroid state by 12 months postpartum
  - 25% of women present with classical form
  - 25% of women with isolated thyrotoxicosis
  - 50% of women with isolated hypothyroidism
- Thyrotoxicosis phase typically occurs 2 – 6 months postpartum
- Thyrotoxicosis resolves spontaneously
- Hypothyroid phase occurs from 3 – 12 months postpartum with 10-20% of cases resulting in permanent hypothyroidism
  - Some evidence to suggest higher rates of this

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PPT

- Autoimmune disorders associated with the presence of thyroid antibodies (TPOAb and TgAb), lymphocyte abnormalities, complement activation, increased NK cell activity, specific HLA haplotypes
- Risk factors:
  - TPO Ab positive
  - History of autoimmune disease (T1DM – 3-4x risk of general population)
  - Women with previous history of PPT (70% change with future pregnancy)
- Thyroid Ab positive in first trimester -> PPT risk of 33-50%
  - Highest Ab titre associated with highest risk of PPT
- PPT reflects rebound of immune system in postpartum period after relative immune suppression of pregnancy

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PPT presentation

- Painless thyroiditis
- Thyrotoxic phase - most women asymptomatic or mildly symptomatic
  - Reported symptoms include irritability, heat intolerance, fatigue and palpitations
- Hypothyroid phase – frequently more symptomatic
  - Cold intolerance, dry skin, fatigue, impaired concentration, paresthesias

- Measure TFT 6 – 12 weeks post partum and at 6 months in women at high risk
- Measure TFT in women with symptoms e.g. anxiety, poor sleep, palpitations

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PPT vs Graves'

- Very important (and can be challenging) to differentiate thyrotoxicosis caused by PPT vs Graves'
  - Conditions have very different clinical courses and different management approaches
- In general:
  - Thyrotoxicosis >6 months more likely Graves'
  - TSHrAb positive in nearly all Graves', typically negative PPT (some mixed-type is seen however)
  - Elevated T4:T3 ratio suggests PPT
  - Physical stigmata of Graves' (e.g. goitre with bruit, orbitopathy) diagnostic when present
  - Technetium scans assist with differentiation (possible in breastfeeding in discussion with nuclear medicine department – precautions need to be taken)

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PPT management

- Treatment is based on trend of TFTs with 4 – 8 weekly monitoring
- Thyrotoxic phase
  - ATDs not indicated as destructive thyroiditis (i.e. hormone synthesis not increased)
  - Beta blockers can be used for symptom management if required
  - Following resolution of thyrotoxic phase, TSH should be measured 4-8 weekly (or if new symptoms develop) to screen for the hypothyroid phase
- Hypothyroid phase
  - Thyroxine started in women with significant symptoms, if lactating or actively attempting pregnancy
  - If treatment not initiated, check TSH levels every 4 – 8 weeks until TFTs normalize
- If thyroxine commenced, attempt discontinuation of therapy after 12 months with slow tapering (however avoid if woman is pregnant or actively attempting pregnancy)

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PPT follow-up

- 10-50% of women in whom the hypothyroid phase of PPT initially resolves will ultimately develop permanent hypothyroidism therefore recommendation for annual TSH testing (or earlier if symptomatic)
- Treatment of euthyroid thyroid-Ab positive pregnant women with thyroxine to prevent PPT is ineffective and not recommended

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Take home points: Gestational diabetes

- GDM is diagnosed per universal screening at 24 to 28 weeks' gestation on a 75g pregnancy oral glucose tolerance test (OGTT) if any one of the following are abnormal: fasting glucose ≥5.1mmol/L, 1-hour glucose ≥10.0mmol/L, 2-hour glucose ≥8.5mmol/L.
- Women with high risk factors for GDM are recommended to undergo early screening with an early OGTT. Women with moderate risk factors have the option for a fasting glucose and, if clinically indicated, an OGTT. Diabetes in pregnancy is diagnosed on an OGTT with a fasting plasma glucose of ≥7.0mmol/L or 2-hour glucose of ≥11.1mmol/L. Early GDM remains a controversial entity however, in many centres would be treated. Treatment of early GDM is now supported by recent trial data.
- GDM treatment targets are centre-dependent and are: fasting blood glucose level ≤5.0 – 5.5mmol/L and 2-hour post-prandial blood glucose level <6.5 – 6.7mmol/L.
- Post-partum screening with an OGTT at 6 – 12 weeks post delivery is recommended. Women with GDM are at increased risk of developing type 2 diabetes in future and are recommended to undertake 2 yearly fasting plasma glucose and HbA1C testing.

Take home points: Thyroid disease in pregnancy

Western Health

Hypothyroidism

- Overt hypothyroidism in pregnancy is associated with significant maternal and neonatal adverse outcomes and requires adequate levothyroxine replacement and close follow-up throughout pregnancy.
- In women with pre-existing hypothyroidism, the thyroid is unable to produce the additional thyroxine to meet physiological pregnancy needs. In women with pre-existing adequately replaced hypothyroidism, levothyroxine dose is increased by 30% as soon as pregnancy is determined with dose adjustments made every 4 – 6 weeks. The TSH aim during pregnancy is 0.1 – 2.5mU/L. Levothyroxine dose is then reduced to pre-pregnancy dose immediately postpartum.
- Pre-pregnancy planning enables levothyroxine titration to aim for a TSH <2.5mU/L prior to falling pregnant.

Subclinical hypothyroidism

- Subclinical hypothyroidism is controversial in its significance and need for treatment. Thyroid function tests should not be routinely ordered in pregnancy except in case of symptoms of thyroid dysfunction or personal history of thyroid disease, head and neck irradiation, prior thyroid surgery, co-morbid autoimmune conditions, recurrent miscarriage or use of amiodarone or lithium.
- Treatment with levothyroxine therapy is initiated when the TSH level is above the pregnancy specific range or, if a pregnancy specific TSH range is not available, a TSH > 4.0 mU/L.

Take home points: Thyroid disease in pregnancy

Western Health

Hyperthyroidism

- Thyrotoxicosis in pregnancy in most commonly due to gestational hyperthyroidism or Graves' disease.
- Gestational hyperthyroidism is usually transient and often associated with hyperemesis gravidarum. Management is supportive with consideration of beta-blockers.
- Pregnant women with Graves' disease (pre-existing or newly identified in pregnancy) require early specialist multi-disciplinary team management. Significant maternal thyrotoxicosis requires urgent endocrine input and management to reduce risk of potential serious maternal and neonatal complications.

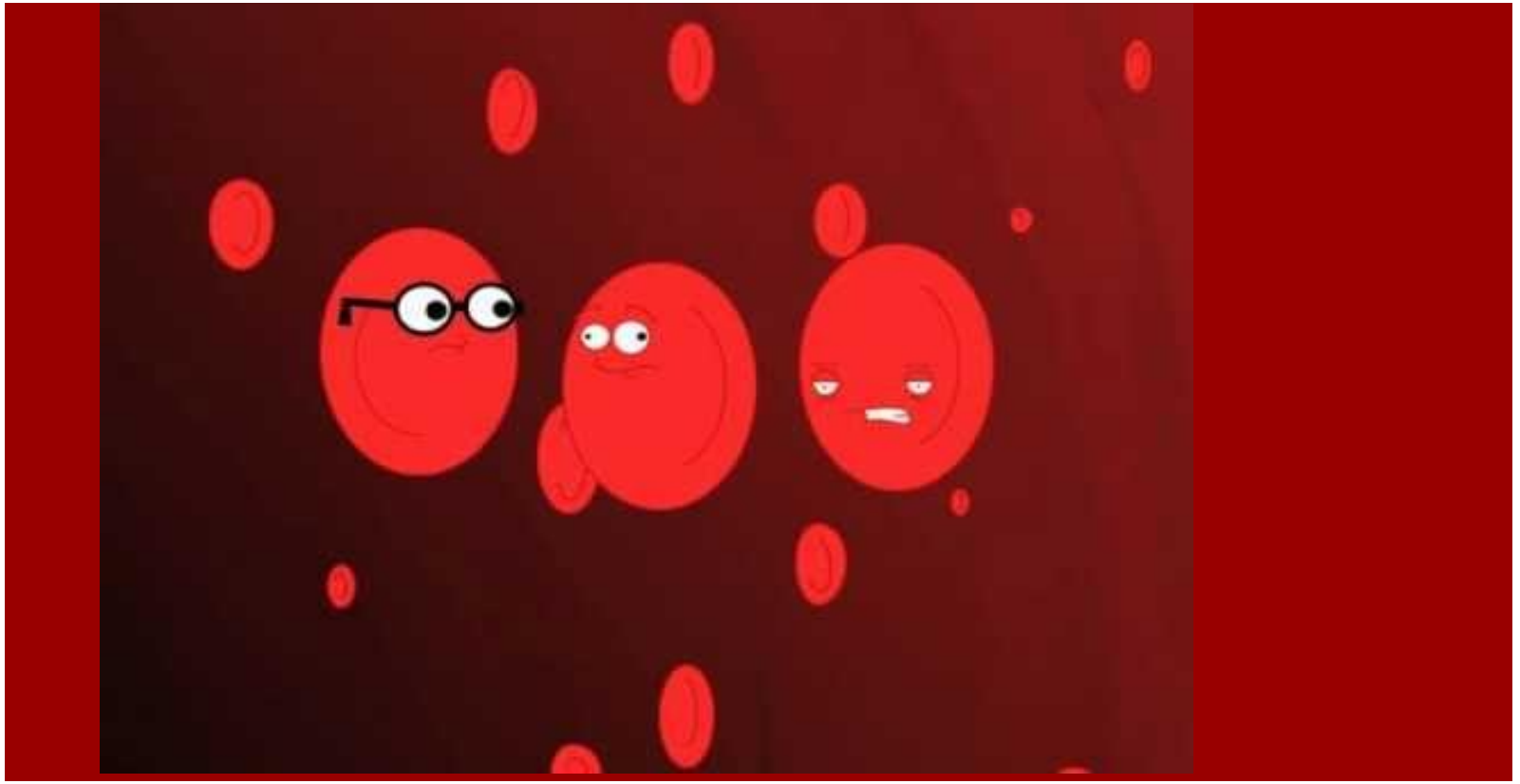
Postpartum thyroiditis

- Postpartum thyroiditis is a destructive thyroiditis caused by an autoimmune mechanism and can present as either transient hyperthyroidism, transient hypothyroidism or transient hyperthyroidism followed by hypothyroidism and recovery. Symptoms can mimic postpartum fatigue or postpartum depression.
- The thyrotoxic phase of postpartum thyroiditis must be differentiated from Graves' disease.
- Management of thyrotoxic phase is usually symptomatic while management of hypothyroid phase requires thyroxine.

Speaker

Northern Health

Dr Vanessa Manitta is a Clinical and Laboratory Haematologist with a special interest in antenatal and obstetric haematology, including prenatal counselling and investigation of thalassemia/haemoglobinopathy. She currently practices as a consultant haematologist and medical obstetrics physician at Northern Health and Mercy Health.



Obstetric Haematology

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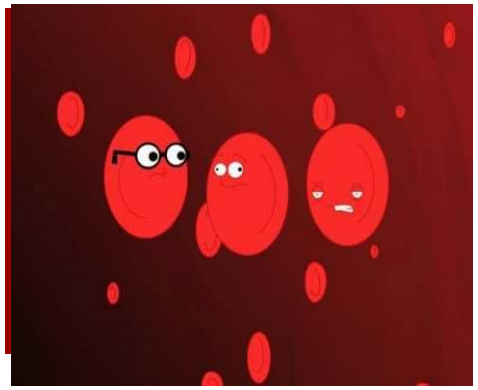
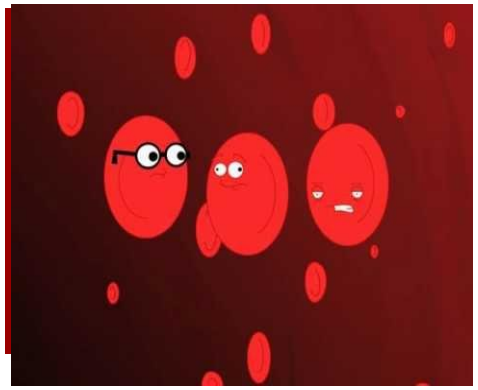
Mercy Hospital for Woman
Northern Private Hospital

Topics



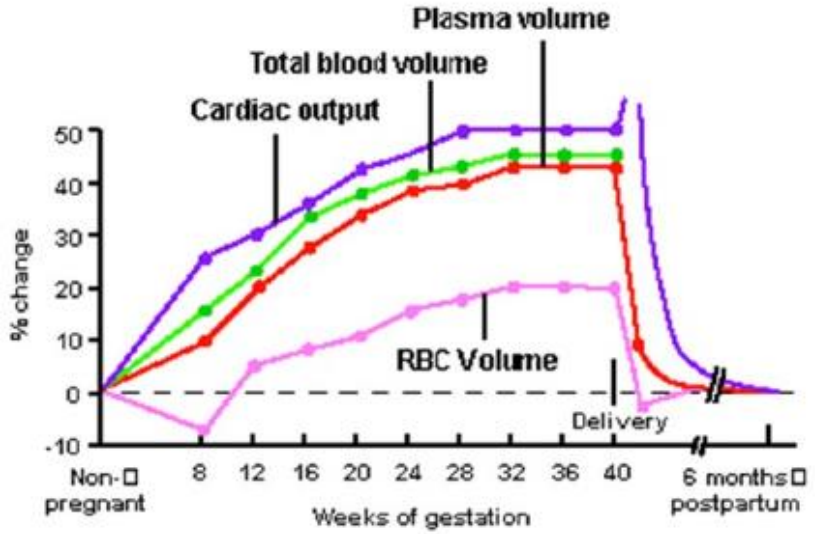
- Anaemia in pregnancy - iron deficiency
- Antenatal thalassemia screening in primary care
- Thrombocytopenia in Pregnancy: ITP vs GT
- Venous Thrombosis – Diagnosis and Initial management

Anaemia in pregnancy



- Commonest haematological disorder in pregnancy
  - prevalence rate: 25% of pregnant women in Aus
- Definition:
  - Hb <120g/L Non pregnant female
  - Hb <110g/L 1st and 3rd trimester
  - Hb < 105g/L 2nd trimester

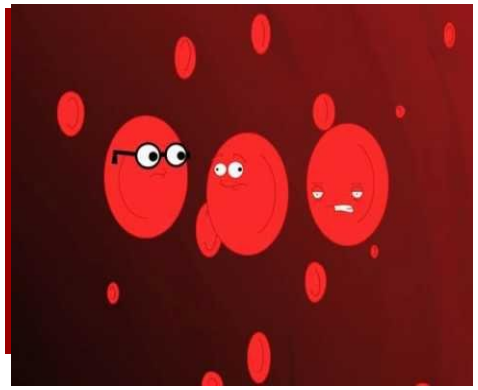
  (plasma volume increases >Red cell mass)
  - Hb <100g/L Post partum female



- **Hb <100g/L at any stage of pregnancy**

indicates anaemia

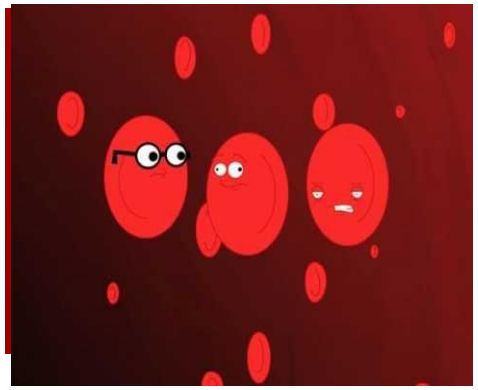
Causes of Anaemia in Pregnancy



- **Blood loss** (acute or chronic)
- **Increased red cell destruction**
  - Inherited haemolytic anaemia (HS, thalassemia)
  - Acquired haemolytic anaemia (AIHA, HUS, TTP, HELLP)
- **Decreased red cell production**
  - Iron deficiency
  - B12/folate deficiency
  - Primary bone marrow disorders
  - Chronic disease (renal failure, Hypothyroid)

- **90% of cases of anaemia in pregnancy are due to iron deficiency**

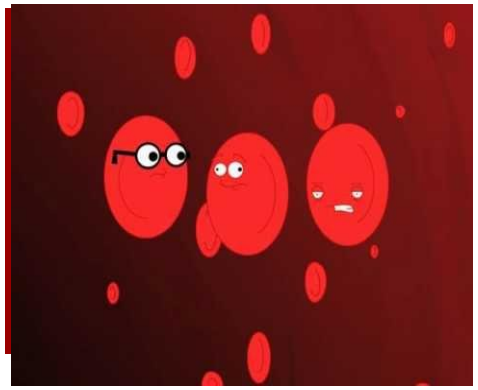
Iron requirements during pregnancy



- Many non-pregnant women have depleted or low iron reserves prenatally
- Physiological demand for iron is 3x greater antenatally
  - Expansion of red cell mass, uterus and placenta
  - Requirement of Foetus (unaffected even if mother is in iron deficient state)
  - Replace blood loss at delivery
- 2nd and 3rd trimester: Iron absorption in gut not sufficient to meet the increased iron demand towards the end of pregnancy

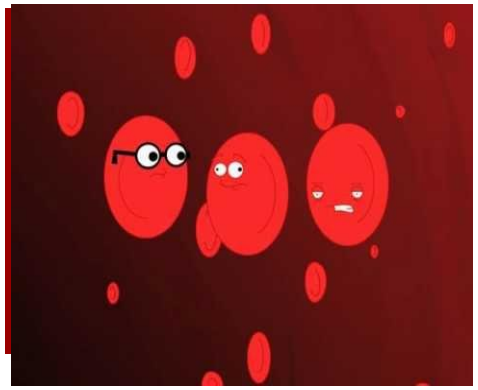
Additional 1000mg -1200 mg iron required in total during entire pregnancy

Does it matter?



- **Maternal effects**
  - Reduced physical capacity: fatigue, reduced energy
  - Reduced mental performance
  - Poor tolerance of blood loss at delivery
  - Increased probability of blood transfusion
  - Increased postpartum depression/emotional instability
- **Pregnancy outcome**
  - Increased rates of prematurity (severe anaemia)
  - IUGR (Severe anaemia)
- **Foetal effects**
  - Impaired psychomotor/mental development???

Case presentation



- 29 year old female, Sri Lankan background. G4P3, 6 weeks gestation.

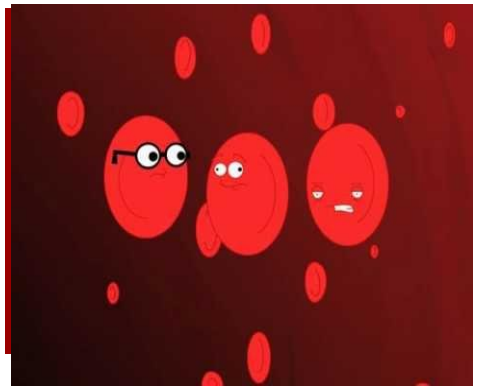
Booking bloods:

Hb 110 g/L (110 – 160g/L)
MCV 78 (80-97fL)

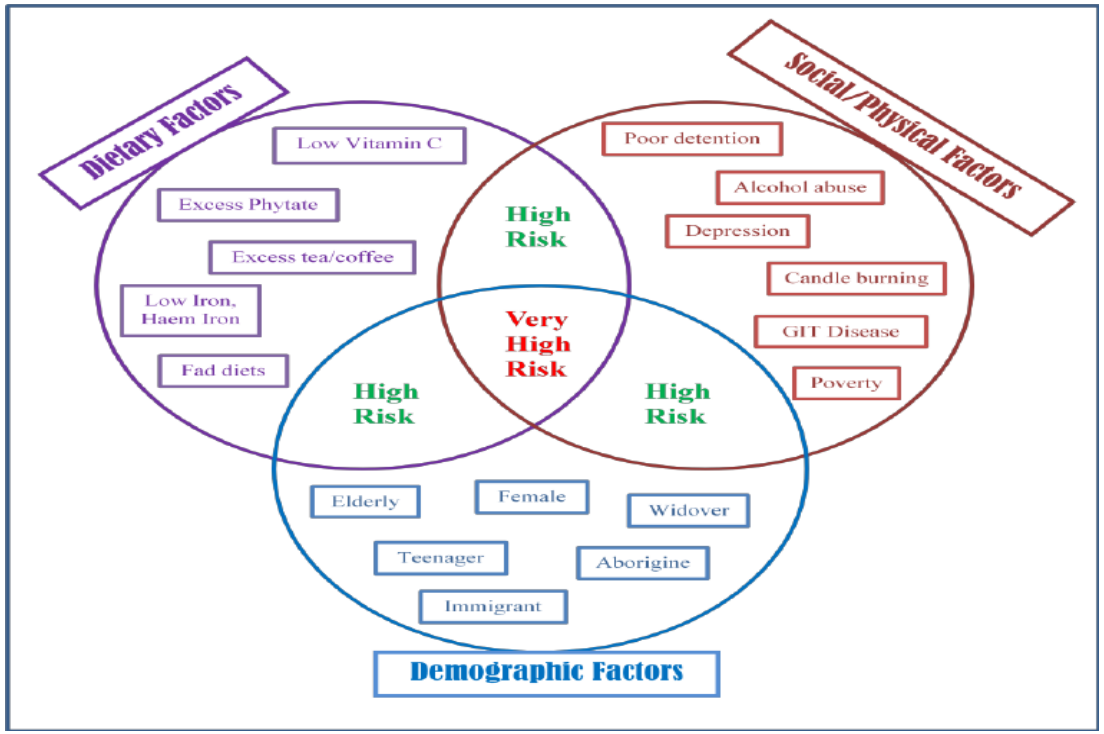
Serum Fe	3	(9-32umol/L)
Transferrin	2.5	(1.81 - 3.31 g/L)
Transferrin sat	13%	(15-50%)
Ferritin	42	(30-250ug/L)

Is she iron deficient?

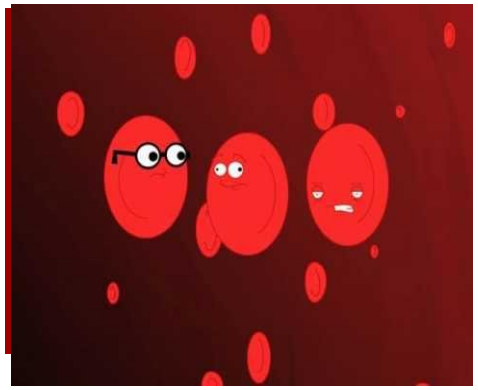
Diagnosis of Iron deficiency



- Thorough history
  - **Causes**
    - Chronic blood loss (menorrhagia, GI loss bleeding disorders)
    - Increased demands (pregnancy, lactation, rapid growth)
    - Malabsorption of iron (gastric surgery, achlorhydria, coeliac disease, IBD)
    - Inadequate diet intake (vegans, vegetarians, old age)
  - **Risk factors**
    - Younger age (<18 years)
    - Multiparity
    - Previous iron deficiency
    - Shortened pregnancy interval
    - Socioeconomic status
    - Poor nutrition
    - GIT absorption issues
    - Nationality



Diagnosis : The FBE



- Clue is in the FBE red cell indices and blood film

- May or not have anaemia. (Iron deficient state vs iron deficiency anaemia)
  - **MCV Mean Corpuscular Volume =** Average volume of the RBC (Size)
    - Microcytic (<80fL) = small RBC
  - **MCH Mean corpuscular Haemoglobin =** Hb amount per RBC
    - Hypochromic (<27pg/cell) = amount Hb < normal

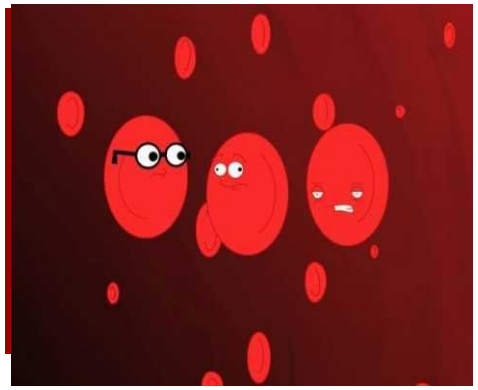
Microcytic Hypochromic = MCV <80fL MCH <27pg/cell

- Reduced size of red cells and amount of Hb per cell
- Can be seen prior to development of anaemia in iron deficient states

Differential diagnosis: Thalassemia/Haemoglobinopathies

- Those with anaemia OR low MCV or MCH; or from high risk demographic for thalassemia
  - Request Hb Electrophoresis +/- DNA studies for alpha thalassemia
  - Request ferritin as well

Interpretation of FE studies



Serum Fe:

- Fluctuates with oral iron intake (false normal with Fe supplements or Fe meal)
- Diurnal (higher in morning)

Transferrin:

- Carrier molecule for iron; amount of iron capable of being transported in the blood
- Increased in late pregnancy (estrogen)
- **Falsely low in acute or chronic disease**

Transferrin Saturation = FE/TIBC= low in IDA and pregnancy.

T sat <20% defines low iron availability

In summary:

- **above parameters are not specific or sensitive enough to diagnose Iron deficiency**

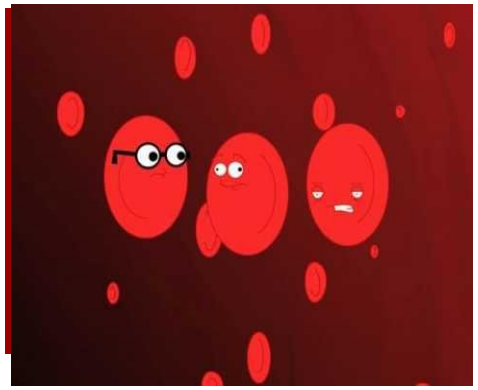
Serum Ferritin

Most accurately reflects iron stores

Ferritin <30 g/L is diagnostic of iron deficiency at any stage of pregnancy

Ferritin 30-100 may indicate low iron stores in the presence of inflammation/infection

Back to the case



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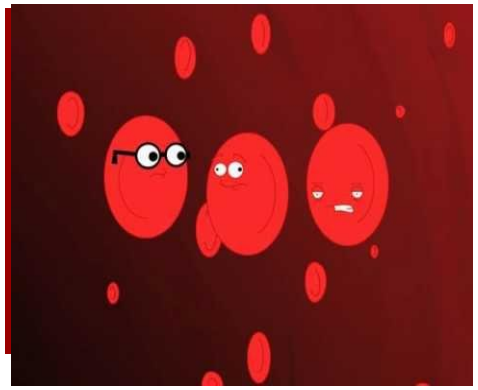
MCV	78	(80-97fL)
Serum Fe	3	(9-32umol/L)
Transferrin	2.5	(1.81 - 3.31 g/L)
Transferrin sat	13%	(15-50%)
Ferritin	42	(30-250ug/L)
CRP	5	

- Risk factors: eats red meat (minimally); shortened pregnancy interval (3 children under 5)
- Microcytic, with normal ferritin. No inflammation.
  - NOT IRON DEFICIENT
  - But at risk of developing during pregnancy due to increased iron requirements
  - ? Thalassemia. Request Hb electrophoresis +/- DNA studies for alpha thal
- **Repeat FBE and Fe studies at 26. (routine repeat at 26-28/40 and 36/40 in all antenates)**
  - 26/40: Hb 105 (105g/ - 140g/L) Ferritin 15
  - What do you do?

Management of Iron deficiency



- Depends on:
  - severity of anaemia
  - gestational age
  - presence of any other additional risk factors

1). Dietary advice + Iron supplementation (Oral or IV)

Dietary advice

- Haem iron (animal sources) 2-3x absorbed than non-haem iron (vegetables and cereals)
- Vitamin C enhances absorption
- Foods that may interact or inhibit absorption
  - Calcium (dairy products); Tea and coffee; Chocolate

- Dietary modification useful for **prevention** of iron deficiency: **not shown to be effective in correcting established iron deficiency**

Supplemental Iron Options

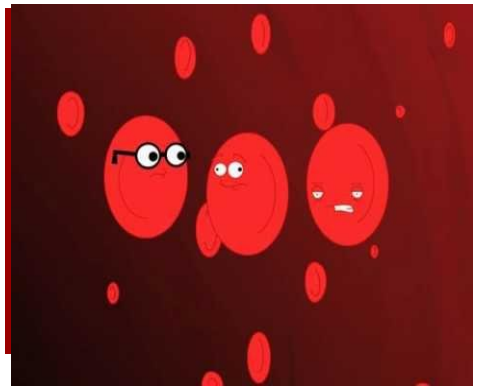
- >100 oral preparations containing iron available :
- Prevention of iron deficiency : 30-60mg elemental iron/day
- Treatment dose : 100-200mg elemental iron /day (poorly tolerated): Aim 60mg daily
- most natural prep have insufficient elemental iron

"Natural" oral iron preparations	Elemental iron content in mg	No of tablets / amount in mL to achieve recommended daily dose (48-80 mg)
Iron melts	5 (as ferrous fumarate) + 0.2 mg folate, ascorbic acid 50 mg, vit B_{12} 0.1 mg	8-16 tablets
Herron one a day iron formula	5 (as ferrous fumarate) + 0.4 mg folate, ascorbic acid 50 mg, vit B_6 10 mg, vit B_{12} 0.02 mg	8-16 tablets
Blackmore's Bio Iron	5 (as ferrous fumarate) + 0.16 mg folate, ascorbic acid 100 mg, vit B_{12} 0.05 mg, nettle herb powder 100 mg	16 tablets
Blackmore's Pregnancy and Breastfeeding Gold	5 (as ferrous fumarate) + 25 mg folate, ascorbic acid 30 mg and other vitamins and minerals	16 tablets

NAME (Manufacturer)	TABLET	FORMULATION	ELEMENTAL IRON CONTENT
FERRO-LIQUID (AFT pharmaceuticals) PBS listed		Ferrous Sulphate Oral solution	30 mg/5 mL
FEFOL® Iron and folate supplement (Pharm-a-care)		Ferrous Sulphate 270 mg Folic acid 300 mcg Delayed release capsule	87.4 mg
Ferro-f-tab (AFT pharmaceuticals)		Ferrous Fumarate 310 mg Folic acid 350 mcg	100 mg
Ferro-tab (AFT pharmaceuticals)		Ferrous Fumarate 200mg	65.7 mg
FERRO-GRADUMET (Abbott)		Ferrous Sulphate 325 mg Modified release tablet	105 mg
FERRO-GRAD C (Abbott)		Ferrous Sulphate 325 mg Ascorbic acid 500 mg Modified release tablet	105 mg
FGF (Abbott)		250 mg Ferrous Sulphate Modified release tablet	80 mg
#Maltofer (Aspen Pharmacare)		Iron polymaltose 370 mg	100 mg
#Maltofer Syrup (Aspen Pharmacare)		Iron polymaltose 185 mg Oral solution	50 mg/5 ml

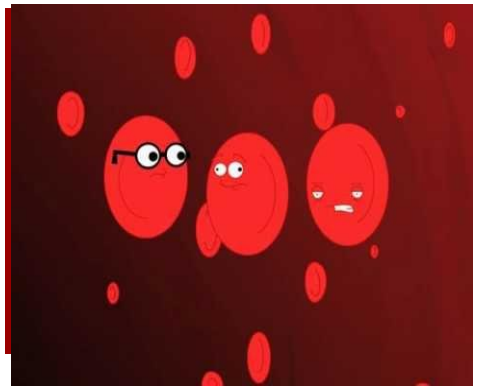
Elevit: 60mg elemental iron + 11 other vitamins and minerals including calcium: increases the risk of constipation and reduces the absorption of iron

Taking oral iron - advice



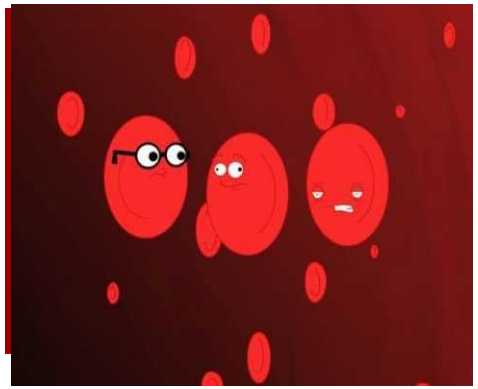
- Commence every 2nd daily (or 2-3 x weekly) and titrate to one daily as tolerated
  - Lower doses may be as effective and better tolerated.
  - Recent studies suggest lower doses (40-80mg elemental iron) or intermittent supplementation (alternate days) may be more advantageous as it maximizes iron absorption due to alterations in hepcidin levels.
- Best taken in the morning, on empty stomach, with source of vitamin C
- Take an hour before or 2 hours after food to improve efficacy
- GIT intolerance (nausea, vomiting, indigestion and constipation)
  - take with food or at night
  - Advice on avoidance of constipation/management
- Avoid milk (calcium), tea, coffee, antacids, phytates (cereals and legumes) within 1 hour of iron supplementation

Back to the case



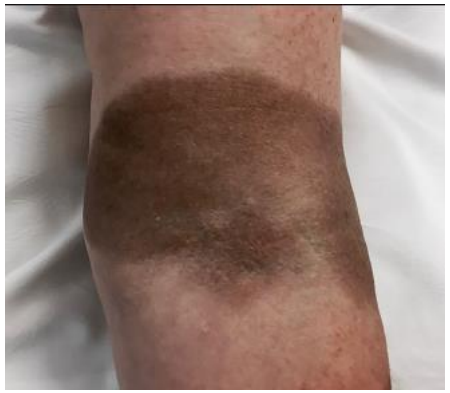
- Advise patient to take FerroGrad C 2nd daily
- Repeat Fe studies and FBE at 30 weeks gestation
  - Ferritin 10; Hb 90g/L
  - Describes constipation with oral Fe
  - When do you refer for an iron infusion?
- **Indications for IV iron**
    - Intolerance to oral iron; unable to absorb orally (GIT surgery)
    - Failed response to trial of oral Fe for 4 weeks
    - Pt with IDA near term (>36 weeks gestation)
    - Anaemia (eg. Hb <100g/L)
- **Contraindications**
    - First trimester pregnancy
    - History of anaphylaxis/reaction to parenteral iron

What types of iron do we give?

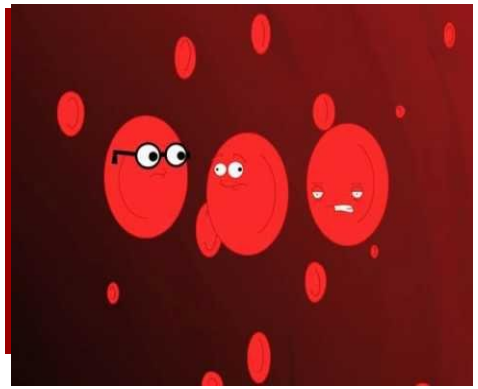


Iron **CARBOXY**maltose	Iron **DERISO**maltose	Iron **POLY**maltose
Dilute in Sodium Chloride 0.9% **Dose 500mg in 100mL** **Dose > 500mg in 250mL** **Dose ≤ 1000mg** Infuse over 15 minutes	**Dilute in 100mL Sodium Chloride 0.9%** **Dose ≤1000mg** Infuse over 20 minutes **Dose 1000mg to 1500mg** Infuse over 30 minutes	**Dilute in 250mL Sodium Chloride 0.9%** **Dose ≤1500mg** Infuse over ~75 minutes **Dose > 1500mg up to 2000mg** Infuse over ~105 minutes

- **Side effects**
  - Headache, dizziness, muscle or joint pain (<10-30%)
  - Chest pain, shortness of breath (<5%)
  - Changes to Blood pressure and pulse (Fishbane Reactions)
  - Severe allergy/anaphylaxis (<0.1%) RISK OF PRETERM LABOUR
  - Hypophosphatemia. (Ferric carboxymaltose)



- Rare: skin staining or brown discolouration : **permanent!!**



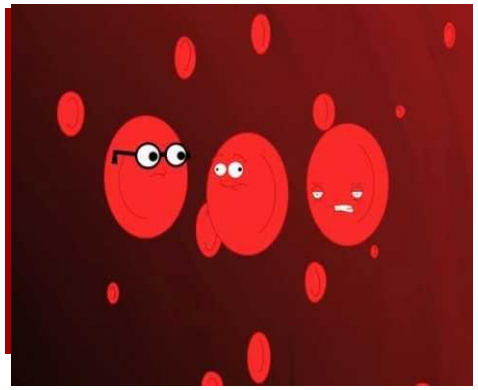
Back to the case

- Iron infusion referral to local hospital
- Hb electrophoresis: Beta thalassemia trait
- What do you do now?

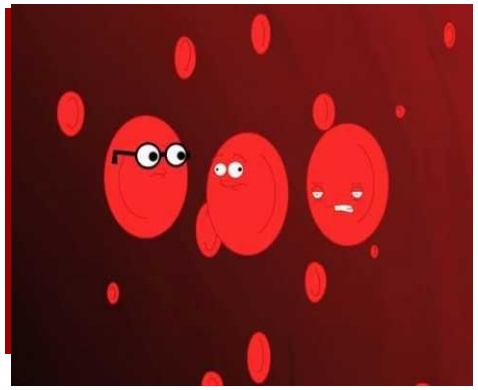
  - Request partner screening for thalassemia
    - Hb 130 g/L. (130-170g/L)
    - MCV. 90 (80-100 g/l) MCH 30 (27-31pg)
    - Hb electrophoresis: Hb S Heterozygote!!

  - What do I do?

Thalassemia

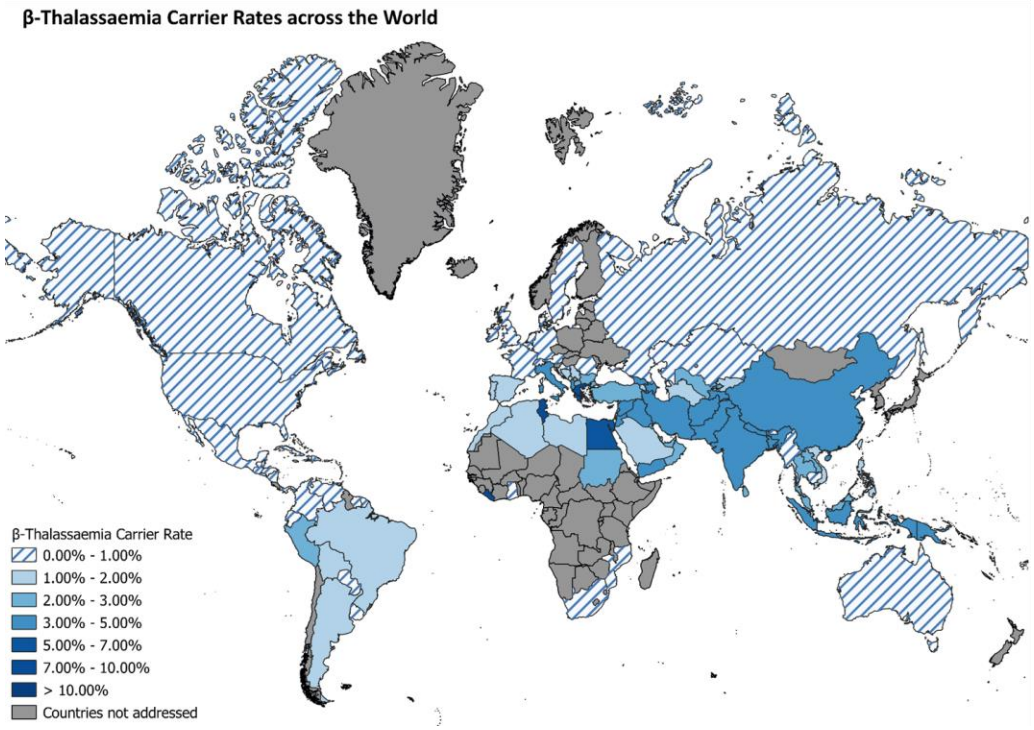


- Most common inherited abnormality in the world
- Detected in approximately 6% of patients of reproductive age in Australia.
- Alpha or Beta chain imbalance in red cells cause ineffective red cell production and increased red cell destruction.
- The severity of the condition will depend on:
  - the number of abnormal genes involved
  - type of mutations
  - ratio of alpha to beta globin chains.
- Depending on the mutation, thalassemia syndromes may result in adverse maternal or foetal outcomes.



How to detect thalassemia?

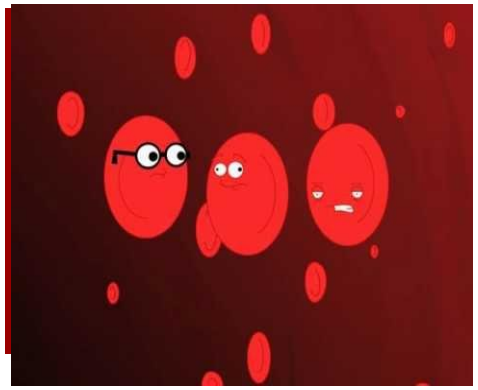
- Many will have low MCV/MCH
- May have anaemia
- **May have normal FBE and film!**
- Family history
- Consider in at risk ethnic groups.



Diagnosis:

- Requires Hb electrophoresis (Beta chain and some alpha)
- DNA studies (generally for alpha mutations)

Antenatal screening for Thalassemia/Haemoglobinopathy



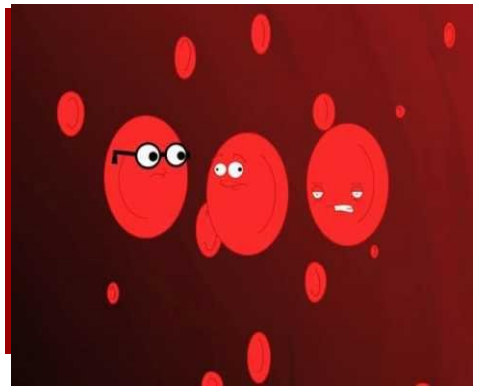
Aim:

- To identify, screen, and offer timely genetic counseling to women and their partners who test positive for thalassaemia/haemoglobinopathy

- Who to offer screening?
  - History of unexplained anaemia
  - Family history of anaemia (unknown cause) or haemoglobinopathy
  - Belonging to an ‘at risk’ ethnic background
  - Women who have MCV ≤ 80fL and/or MCH ≤ 27pg

- Northern Hospital – all antenatal women are screened due to high at risk demographic population

What to do in primary care practice?

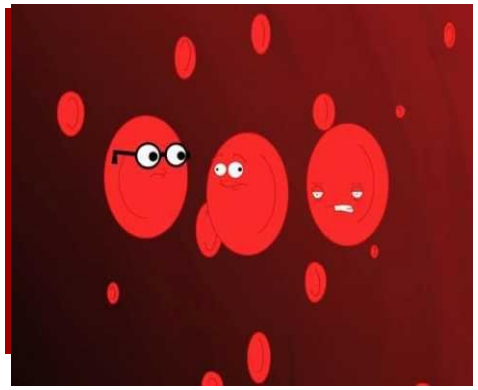


Preconception diagnosis is crucial

Primary care has the most important role.

- Preconception screening if possible
  - Prenatal counselling optimal
  - Aim to screen patient and partner, provide counselling, offer prenatal testing (CVS or amniocentesis) before 14 weeks gestation!!!

- Early antenatal screening



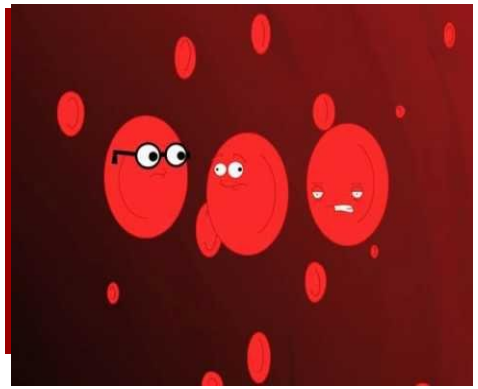
What to do in primary care practice?

At confirmation of pregnancy (Ideally prenatally):

- Assess woman's history – nationality, ancestors
- Thoroughly assess family and partner history for risk factors.
- Review Past FBE results
- Confirm if she has had previous testing for haemoglobinopathies. Obtain a copy.
- Assess if partner has had testing and confirm status.

- What tests to order?
  - FBE, FE studies, Hb electrophoresis. +/- DNA alpha gene studies
  - If any positive result, or if known thalassemia, request partner testing
    - FBE, FE studies, Hb electrophoresis +/- DNA studies
    - ON REQUEST FORM: write partner details
    - If high clinical suspicion – order with antenatal bloods or prenatal

When to refer to haematology?



Arrange blood tests of antenate

- FBE
- Hb electrophoresis +/- alpha DNA studies
- Iron studies/CRP

Normal FBE and Hb electrophoresis
No further action
(some carriers of single alpha gene deletions will not be detected)

Low ferritin
If pregnant, proceed with partner testing
Treat for Fe deficiency and retest in 4 weeks

Abnormal FBE
MCV < or = 80 OR MCH < or = 27 pg
+/or
Abnormal Hb electrophoresis

Arrange Partner testing

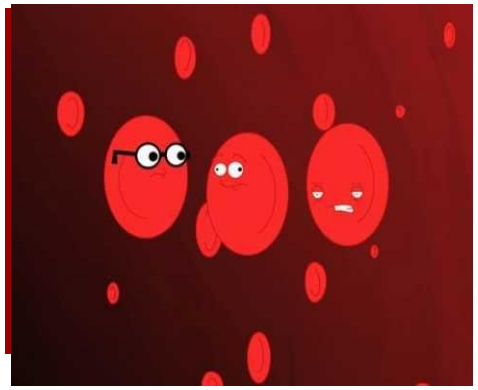
- FBE
- Hb electrophoresis +/- alpha DNA studies
- Iron studies/CRP

Normal FBE red cell parameters and Hb electrophoresis in partner
Couple have low risk of child with severe haemoglobinopathy
Refer to genetic counseling ONLY if patient concerned

Abnormal FBE red cell parameters or Hb electrophoresis in partner with normal ferritin
Couple may be at risk of child with severe haemoglobinopathy

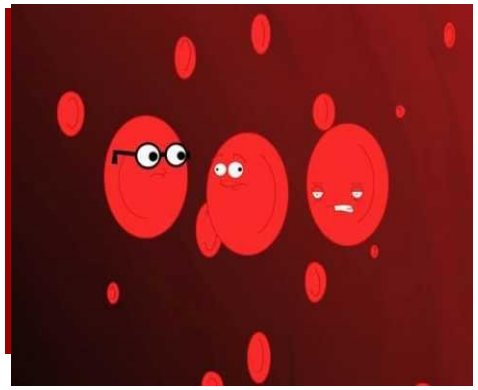
Refer to genetic counseling

Questions?



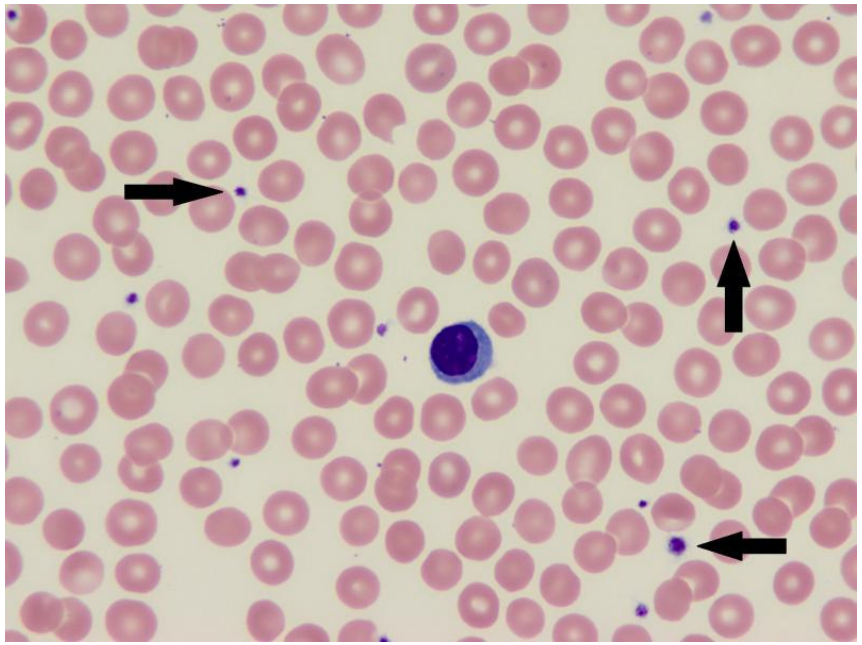
Platelets and pregnancy

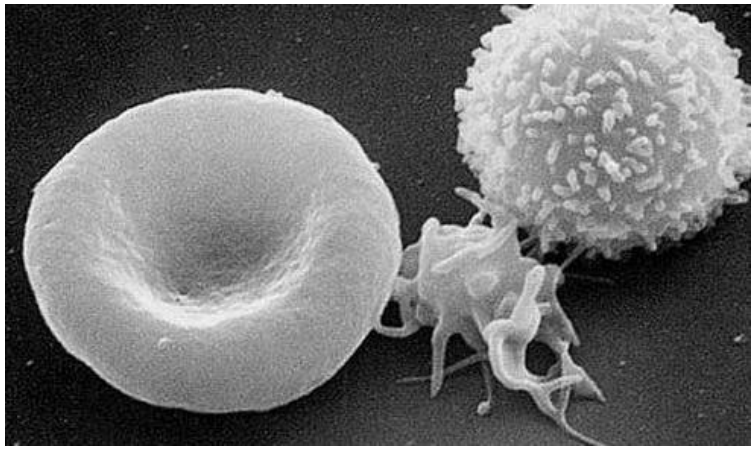
Platelets & Pregnancy



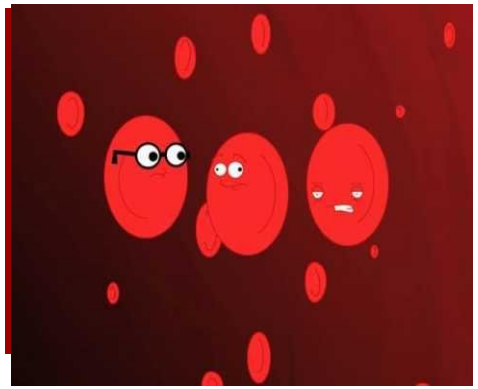
Disorders in platelets :

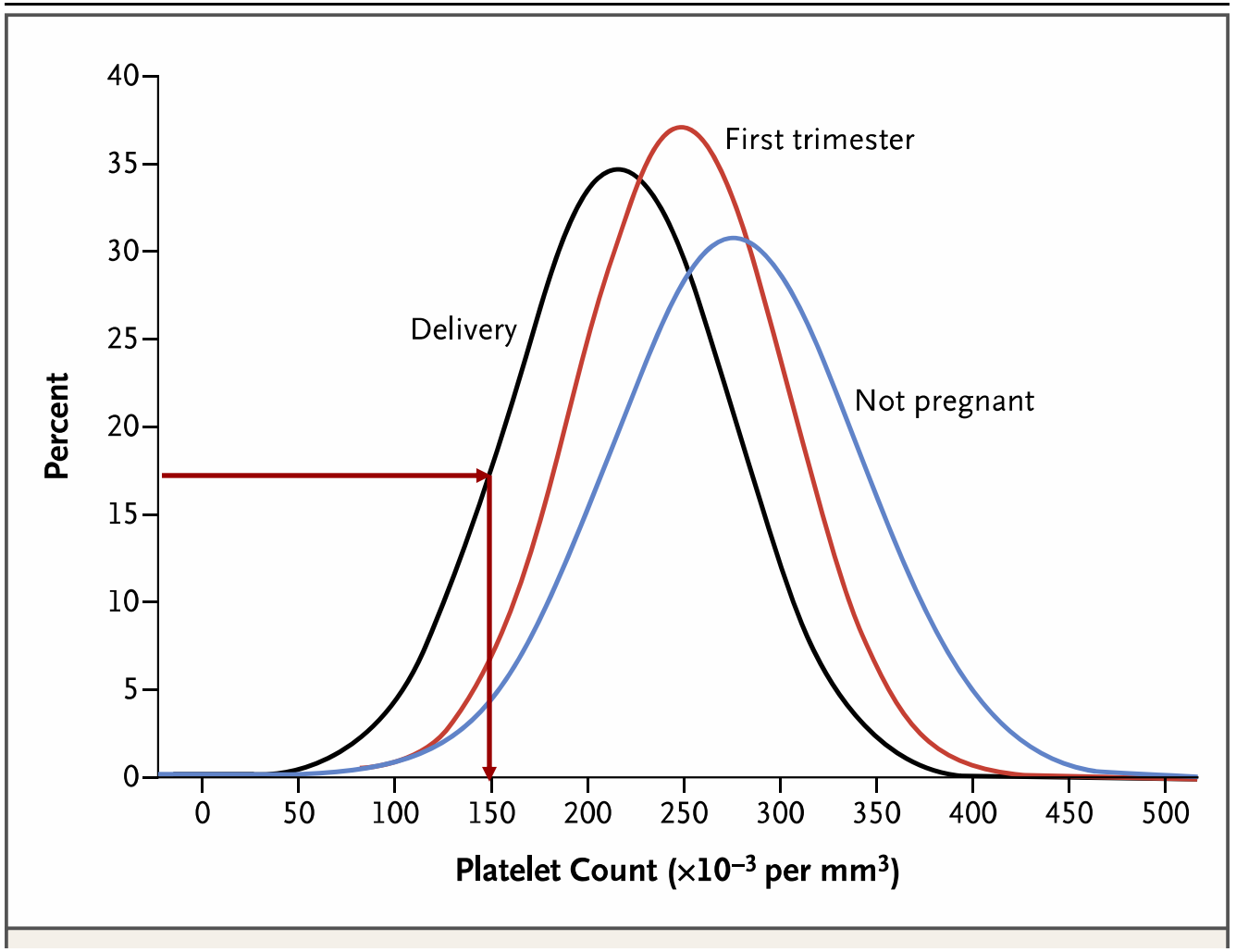
- Thrombocytopenia: 2nd most common haematological abnormality in pregnancy
- Thrombocytosis – unusual in pregnancy; pathological (reactive eg Fe deficiency)
- Most cases are incidental findings on routine FBE.





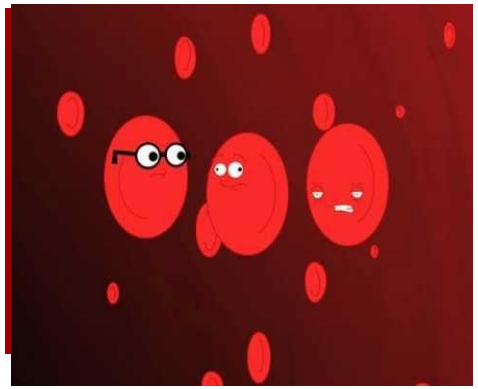
Platelets & Pregnancy





Reese *et al.* NEJM 2018

Causes of thrombocytopenia in Pregnancy



Pregnancy Specific

Gestational thrombocytopenia (70-80%)

Severe Pre-eclampsia (15-20%)

HELLP syndrome (<1%)

Acute Fatty Liver (<1%)

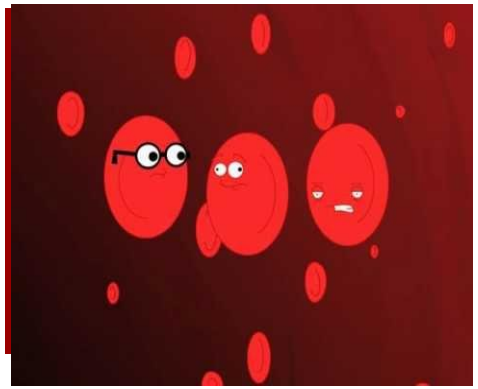
Non Pregnancy Specific

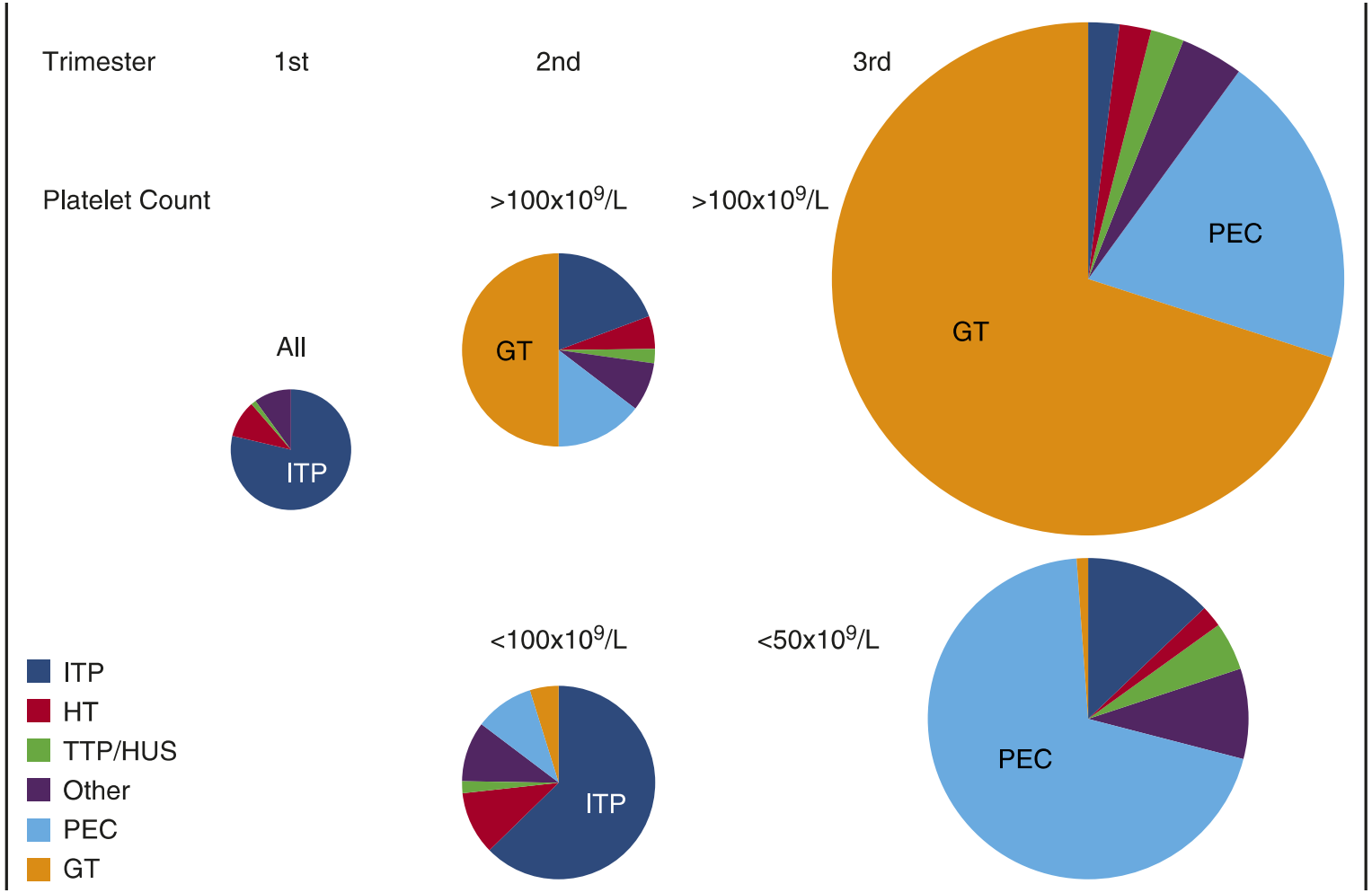
ITP: **Primary (1-4%)**
Secondary (<1%)
Eg Viral (HIV, Hep B, C)
Autoimmune (eg. SLE)
APS syndrome

Thrombotic microangiopathies (<1%)
Eg TTP/HUS
aHUS

Rare causes (<1%)
DIC
Drugs
Type IIB vWD
Congenital/Inherited TCP
Hypersplenism
Bone marrow (MDS, Aplasia)
Nutritional deficiencies
Thyroid disorders

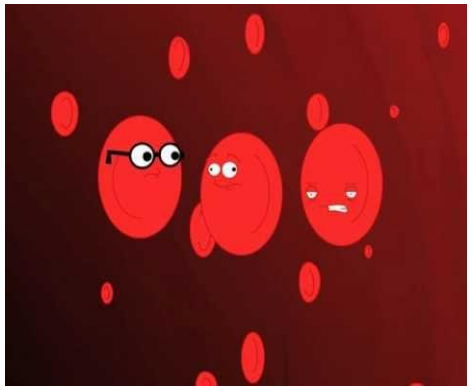
Prevalence of causes of TCP based on trimester of presentation and platelet count





Cines & Levine. Blood. 2017.

Approach to THROMBOCYTOPENIA in pregnancy- **HISTORY**



- **Is it real?**
- **Is it new?**
- **What stage of pregnancy did it present?**
- **Is it isolated?**
- **What is the lowest platelet count?**
  - <70-80 at any time in pregnancy
- **Is there Bleeding?**
  - Past history; family history; evidence of haemostatic impairment needing management
- **Are there Associated features**
  - Hypertension, neurological symptoms, deranged LFTs/renal failure

Approach to THROMBOCYTOPENIA in pregnancy- Investigations

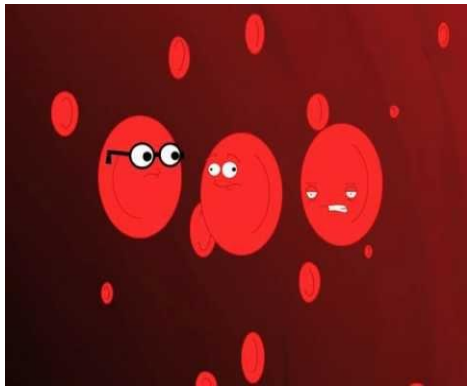


TABLE 2 Initial laboratory tests that may be considered for pregnant women with thrombocytopenia

Initial laboratory tests that may be considered for pregnant women with thrombocytopenia†
Full blood count and reticulocyte count
Peripheral blood film
Optical platelet count (if available)
Coagulation screen
Renal and liver function tests
Thyroid function tests
Direct Coombs test
Antiphospholipid antibodies: lupus anticoagulant, anticardiolipin antibodies, beta 2 glycoprotein 1 antibodies
Antinuclear antibody (ANA)
Hepatitis B/C and human immunodeficiency virus (HIV) serology
Helicobacter pylori
Vitamin B12/folate
Immunoglobulins

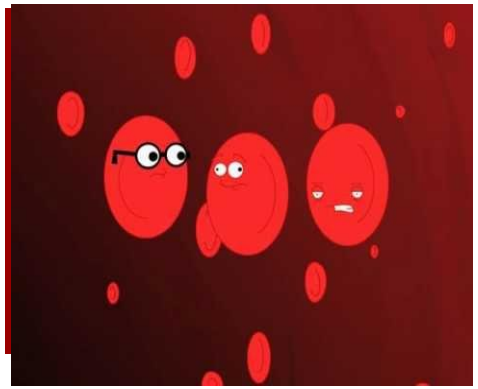
†The level of investigation depends on the severity and gestation at onset of thrombocytopenia.

3rd trimester : Antenates with persistent platelet count < 120: PET screen (BP, LFTS, urinalysis and coagulation screen)

Further tests depending on history (haematologist):

- **TSH:** increased risk of hyperthyroidism in patients with ITP
- **ENA, dsDNA, RF:** further autoimmune screen
- **vwD Type IIB testing (vWF studies)**: consider if:
  - history of bleeding
  - family history of thrombocytopenia
  - unresponsive to ITP therapy
- **Antiplatelet antibodies/Platelet glycoproteins**
  - elevated in both GT & ITP; not recommended for routine use
- **Bone marrow biopsy: in consultation with haematologist**
  - if suspicion of aplastic anaemia, leukaemia or lymphoma.
- **Abdominal ultrasound** : if suspicious for haematological malignancy

Case: Mrs HK



25yo G2P1: 2018 40/40 (Pakistan) emLUSCS with epidural
Patient reports platelets low at the time;
No excess bleeding, no transfusion

Medical/Surgical Hx : Nil
No bleeding history/normal menses
No surgical challenges; No significant family history

(10/40) : Hb 109 MCV 79 (Fe and B12 deficient). Platelets 225

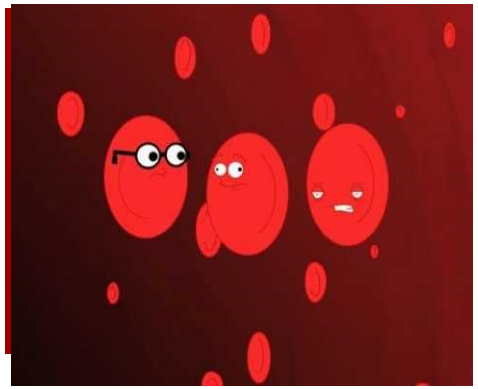
22/40: Plat 140

30/40 : **Platelet 83** **What do we do?**

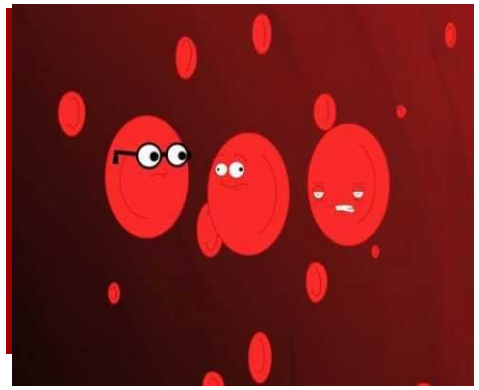
- **Repeat** platelet count 75
- Normal Hb and film (no red cell fragments) ; Normal LFTs, Ues ; neg haemolysis screen (NOT HELLP;TTP, HUS)
- Normotensive; normal protein:creat ratio. (Not pre eclamptic)
- Normal Coags, Viral serology, Autoimmune screen

What is the diagnosis??

Gestational	Immune
4-10% pregnancies	0.1-0.01% pregnancies
Diagnosis of exclusion	Diagnosis of exclusion
Occurs late in gestation (>20 weeks)	Any trimester (indistinguishable from GT if mild or late in pregnancy).
NO TCP outside of pregnancy or early pregnancy (<20 weeks)	TCP present outside of pregnancy or early pregnancy (<20 weeks)
Mild TCP >70 (rarely <50) 1-5% <100 0.1% <80	Plat <70 more likely ITP Most common cause of platelets <50 in 1st & 2nd trim
Foetal/neonatal TCP rare (<2%)	Risk of foetal/neonatal TCP 10-15%
May recur subsequent pregnancies (14x risk)	Count declines significantly in 50% of pregnancies 50% pts require treatment
Postpartum resolution generally within 4-8 weeks	May/may not see improvement in TCP postpartum



Principles of management



- Reduce bleeding complications associated with severe TCP

- Involve multidisciplinary team
  - obstetricians, medical obstetrics, haematologist, anaesthetist, (+/- neonatologist)

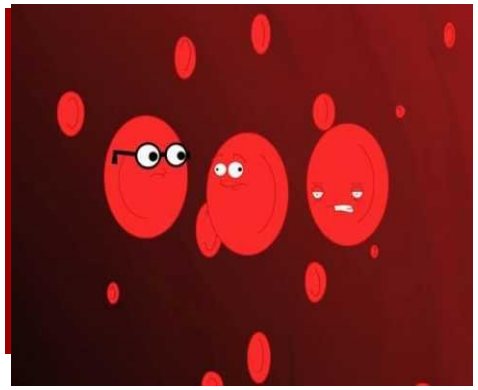
- Antepartum monitoring of platelet count depends on severity of count, gestation and associated cause
    - Mild uncomplicated TCP (platelet count >50 - 100), check platelet count monthly until 28 weeks, fortnightly until 36 weeks, then weekly thereafter

- No evidence that C section is safer for mother or neonate than uncomplicated vaginal delivery in women with significant thrombocytopenia;

  Mode of delivery is determined by obstetric indications

- **Consider Neonate may be thrombocytopenic**

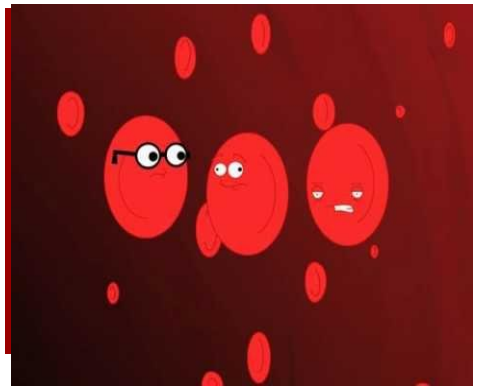
Principles of management



When to refer to haematology?

- Platelet count <100 x 10^9 at any trimester
- Thrombocytopenia has been demonstrated prior to pregnancy
- Known history of ITP
- Family history of thrombocytopenia
- History of bleeding diathesis
- Any thrombocytopenia associated with anaemia, or white cell count abnormalities
- Thrombocytopenia present at **<**20 weeks gestation (preferably persistent demonstrated on >2 FBE reports)

Management of TCP



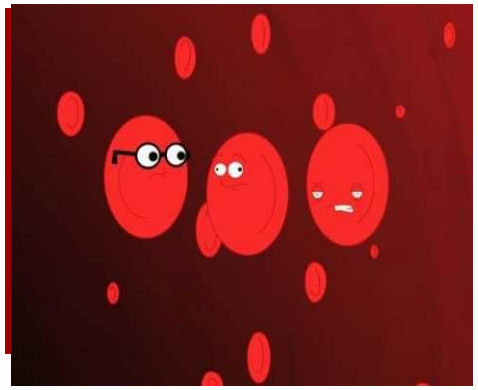
- Depends on cause!
- GT:
  - No therapy if platelet count remains >70-80;
  - Counselling on risks; epidural or not; prior delivery
- If differentiation between ITP and GTP is unclear, treat delivery as per ITP guidelines.
- ITP:

1st line treatment options	2nd line treatment options§	Minimal data to support use	Contraindicated
Prednisone† Initial dose 20–25 mg/day Consider 40–50 mg/day for acute ITP with platelets < 20	Azathioprine¶	Rituximab	Danazol
Intravenous immunoglobulin (IVIg) 1–2 g/kg for 1–2 days	Cyclosporin	Thrombopoietin receptor agonists	Cyclophosphamide
Prednisone plus IVIg if inadequate response to single agent therapy‡	Maternal splenectomy Second trimester		Mycophenolate mofetil
	Platelet transfusion when there is an inadequate platelet count AND significant bleeding or immediately prior to delivery or a planned procedure		Vinca alkaloids
			RhD immunoglobulin

†A trial of prednisone may be considered early in the third trimester in women predicted to require treatment prior to delivery.
‡We recommend combination treatment before moving on to alternative second-line treatment options.
§Second-line treatment should be selected based on time to delivery, side effect profile, clinician experience and maternal preference.
¶Thiopurine methyltransferase (TPMT) testing is recommended prior to commencing azathioprine.

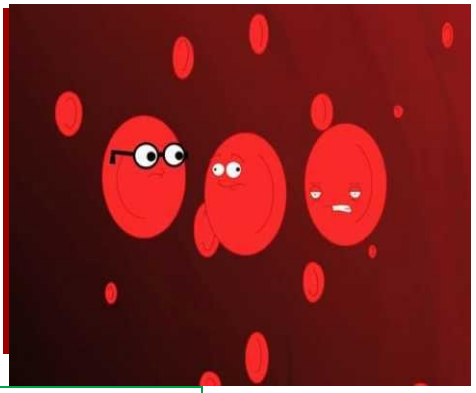

Thrombosis in
Pregnancy and
Puerperium

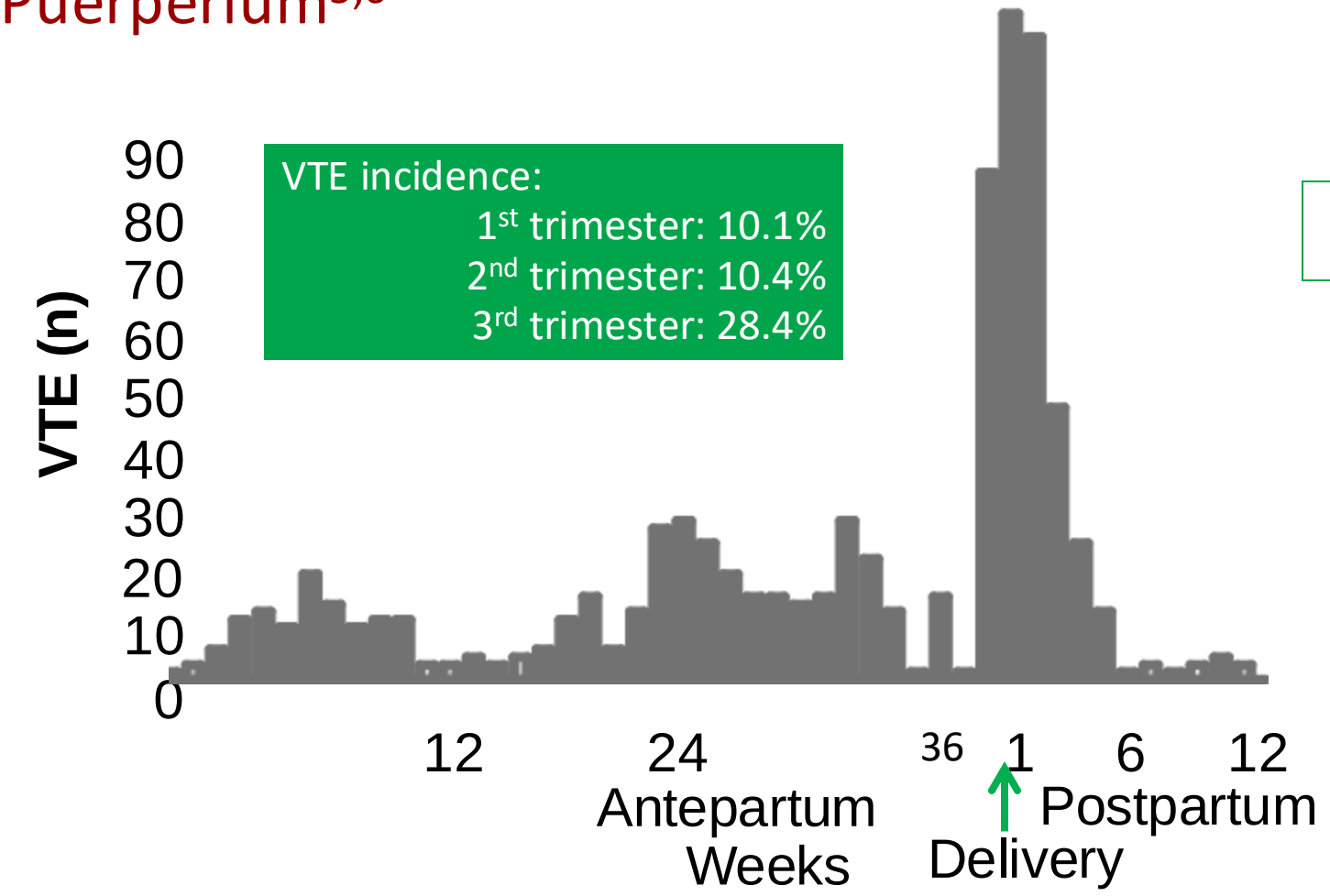
Epidemiology of Obstetric VTE



- 2nd most common cause of direct maternal death in Australia[1]
- Increased risk (4-5 fold) of developing VTE compared to non-pregnant women (risk postpartum estimated 15 – 35 fold)
- Overall incidence of VTE is 1-2 per 1000 pregnancies
  - **DVT Incidence:** more common antenatally than postnatally (0.43 vs. 0.30/1,000 deliveries.
  - **PE incidence** higher postnatally (0.22 vs. 0.06/1,000 deliveries).
  - Maternal mortality caused by VTE approx. 0.48 - 1.1 per 100,000 deliveries

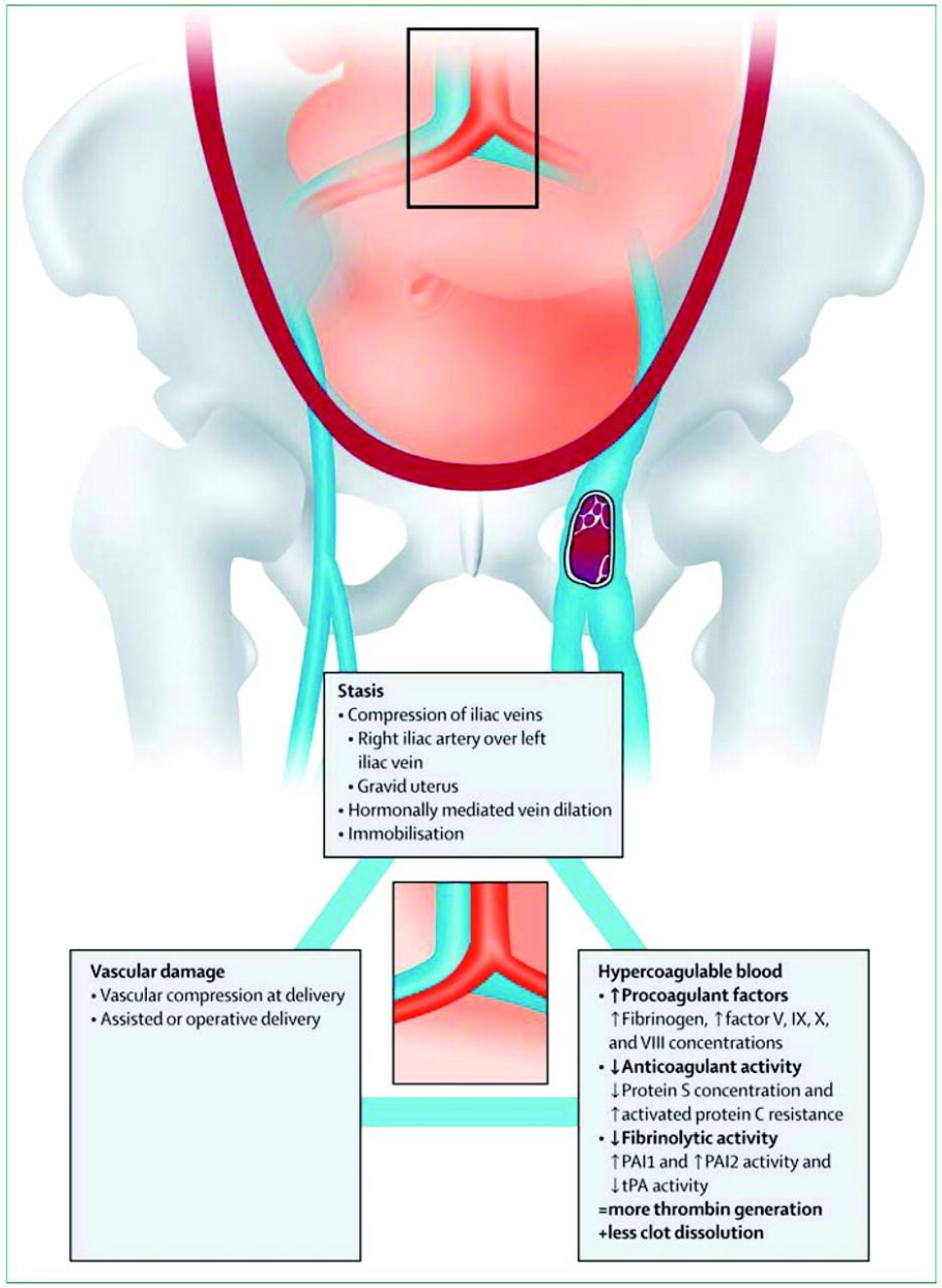
Distribution of VTE in Pregnancy and Puerperium[5,6]

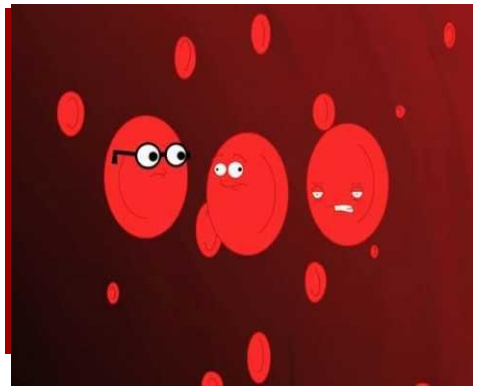


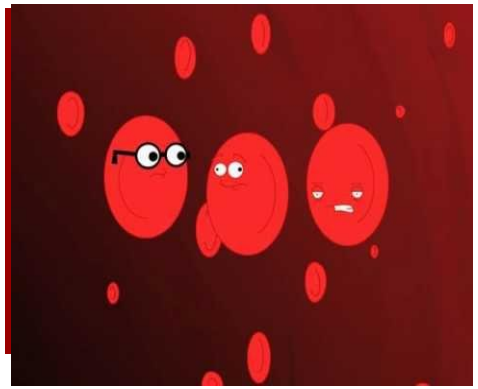


Pathophysiology of VTE in Pregnancy[7]

Virchow's triad: all factors exaggerated in pregnancy!!!







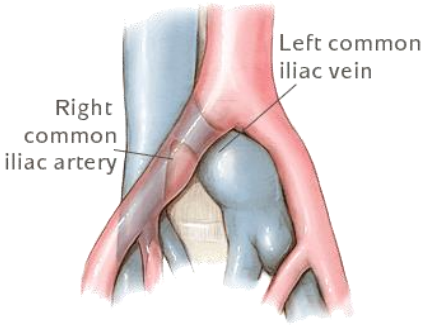
Signs and Symptoms of VTE

DVT

- Unilateral leg Swelling
- Tenderness
- Skin discoloration
- Warm to touch
- Unusual firmness /hardness in the leg
- Prominent superficial veins

70-90% on left (vs. 55% in non pregnant)[5]

70-90% proximal (vs. 9% in non pregnant)[5]

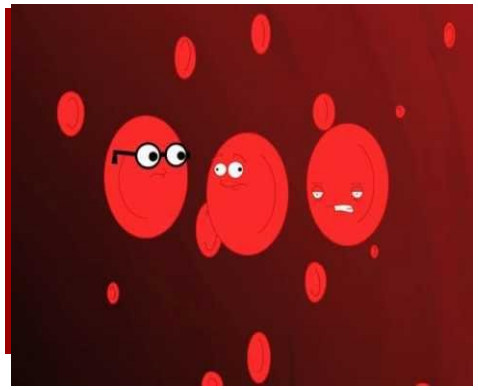


PE

- ***Symptoms***:
  - Dyspnoea (60%)
  - Palpitations
  - Pleuritic chest pain (50%)
  - Fever
  - Haemoptysis (rare)

- ***Signs:***
  - Tachycardia
  - Tachypnoea
  - Hypotension/collapse (massive PE)
  - Cyanosis/hypoxia (massive PE)
  - Right heart failure

Case Study: Mrs. AB



36F G3P2 32/40 gestation;

- 2 day history of left leg swelling
  - PMHx: smoker, obesity

Q1. What other history would you like to know?

- **Risk factors?**

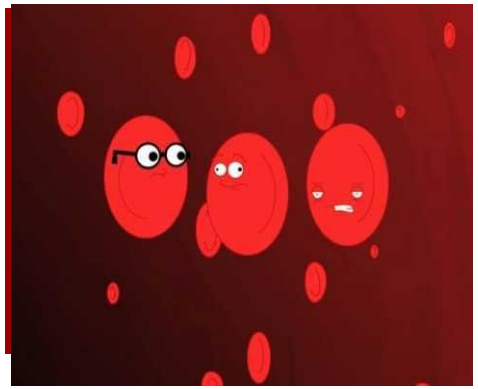
Risk Factors for VTE

aOR for risk of VTE in pregnant and postpartum women compared to pregnant and postpartum women without these risk factors

Risk Factor	AOR	95%CI	Comment
Previous VTE	24.8	17.1–36	n=603
Age >35	1.3	1.0–1.7	pn=256
	1.4	1.0–2.0	n=143 an PE
BMI >30 mg/kg^2	2.65	1.09–6.45	n=129
	5.3	2.1–13.5	
	4.4	3.4–5.7	
	1.7	1.2–2.4	pn=256
BMI >25 mg/kg^2	1.8	1.3–2.4	an=268
	2.4	1.7–3.3	pn=291
	1.7	1.2–2.4	pn=256
Parity 1	4.03	1.6–9.84	n=143 an PE
Parity 2	1.5	1.1–1.9	n=603
Parity 3	2.4	1.8–3.1	n=603
Smoking	2.1	1.3–3.4	an=268
Smoking 10–30/day	3.4	2.0–5.5	pn=291
	1.4	1.1–1.9	n=603
	2.5	1.3–4.7	n=90
Current smoker	2.7	1.5–4.9	n=129
Sickle cell	6.7	4.4–10.1	
	2.5	1.5–4.1	DVT
	1.7	0.9–3.1	PE
Heart disease	7.1	6.2–8.3	
	5.4	2.6–11.3	pn=256
SLE	8.7	5.8–13	
Anaemia	2.6	2.2–2.9	
Varicose veins	2.4	1.04–5.4	
Immobility	7.7	3.2–19	an
	10.8	4.0–28.8	pn
Preeclampsia	2.9	2.1–3.9	
	3.1	1.8–5.3	
Preeclampsia + fetal growth restriction	5.8	2.1–16	
Hyperemesis	2.5	2–3.2	
Assisted reproductive technology	4.3	2.0–9.4	an
Twins	2.6	1.1–6.2	an
Multiple pregnancy	4.2	1.8–9.7	n=603
Preterm delivery <36 weeks	2.4	1.6–3.5	an=109
Antepartum haemorrhage	2.3	1.8–2.8	pn=256
Emergency caesarean section	2.7	1.8–4.1	
Any caesarean section	3.6	3.0–4.3	pn=256
Postpartum haemorrhage >1 L	4.1	2.3–7.3	
Postpartum haemorrhage + surgery	12	3.9–36.9	
Obstetric haemorrhage	9	1.1–71	
Postpartum infection	4.1	2.9–5.7	
Postpartum infection + caesarean section	6.2	2.4-16.2	
Transfusion	7.6	6.2–9.4	

an=antenatal; pn=postnatal; n=number of cases in case-control study;

Source: Royal College of Obstetricians and Gynaecologists. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. Green-top Guideline No.37a. 2009.



Hereditary thrombophilia

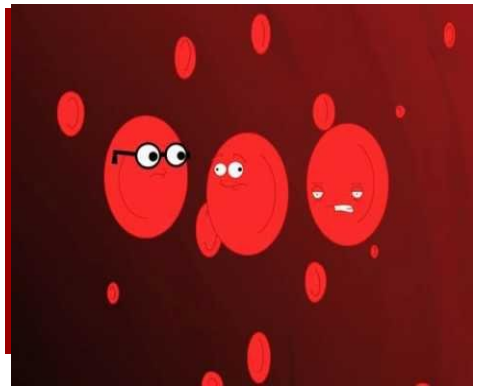
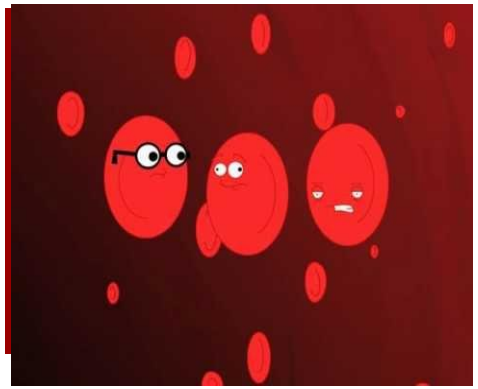


Table 2: Absolute risk of VTE with women with hereditary thrombophilias

Thrombophilia	Family history VTE unknown *	Positive family history VTE with known thrombophilia#
Significant		
Antithrombin deficiency	0.3-4%	3.0-18.0%
Factor V Leiden homozygous	1.3-2.3%	9-17.0%
Factor V Leiden/prothrombin mutation compound heterozygous	5.20%†	1.8-5.5%
Protein C deficiency	0.5-1.8%	1.7-5.0%
Protein S deficiency	0.1-1.0%	2.0-6.6%
Weak		
Factor V Leiden heterozygous	0.2-0.5%	1.5-3.9%
Prothrombin mutation heterozygous	0.2-0.4%	1-2.8%
Family history of VTE with thrombophilia: unaffected controls		0.4-1.4%

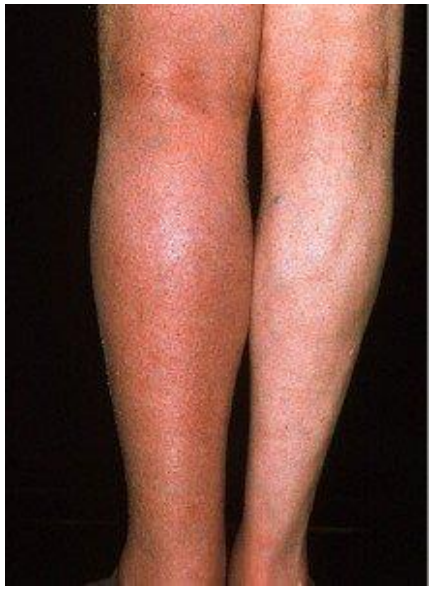
Significant risk factors:

- Prior history of VTE
- a positive family history of VTE
- BMI > 30



Back to Case

- **Leg symptoms:** Erythema, increased warmth, pain/tenderness
- **Personal history:** No Recent immobility? Surgery? Travel?
  No prior history of VTE
  Family history: Unremarkable with no history of VTE
- **Comorbidities**: None
- **System review**: No chest pain, SOB or palpitations

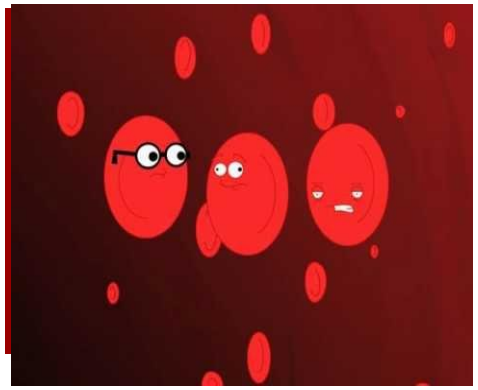


- General
  - BMI 35 kg/m^2
  - BP 100/75 mm Hg ; Pulse 70 bpm
  - Chest clear

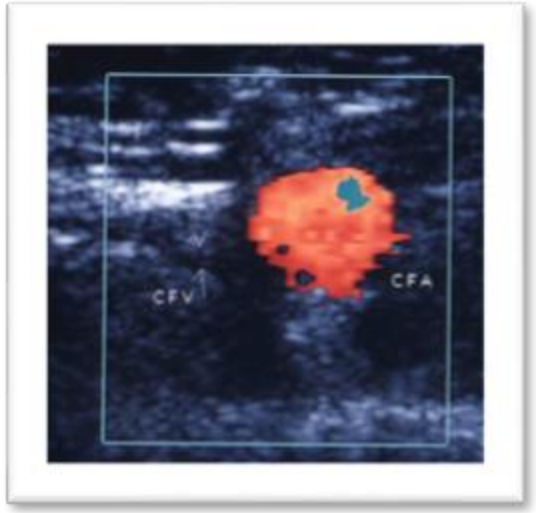
- Lower extremities
  - Left calf swollen
  - No obvious venous distension
  - Mild erythema left leg and warmth
  - Mild tenderness to palpation

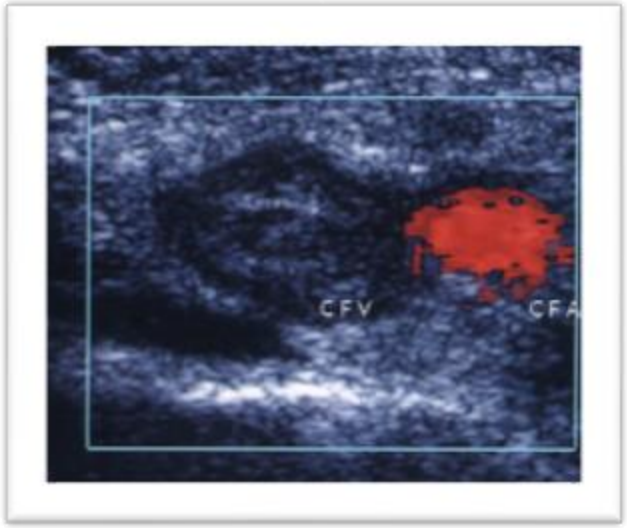
You suspect DVT, What Next?

Investigation for Suspected DVT



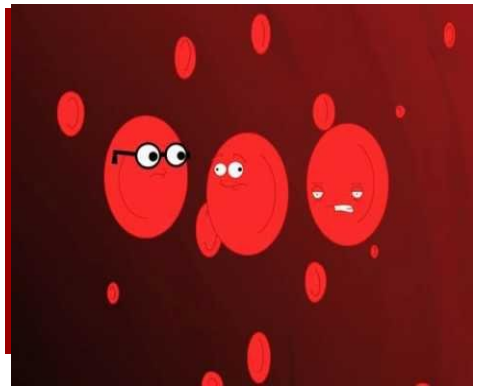
- Compression ultrasound (CUS) of the entire leg should be done.





- When results are negative and iliac vein thrombosis is not suspected, routine surveillance may be a reasonable option (repeat doppler in 1 week)
- When results are negative and iliac vein thrombosis is suspected, consider MRI

Case Study: Mrs. AB



Doppler: Occlusive thrombus within femoral vein, 8 cm long

Q: What other information do you need before starting anticoagulation therapy?

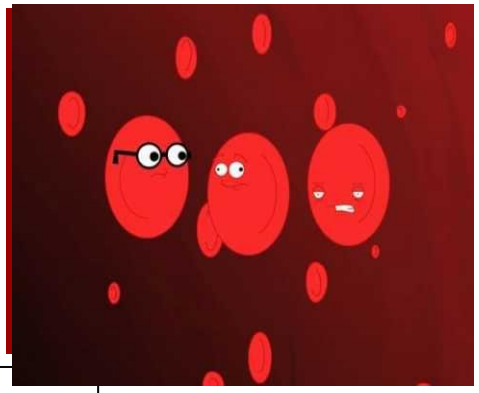
- Full blood count
- Baseline coagulation
- Renal Function
- Liver function

- Important for establishing baseline values
- Detect and monitor any complications during anticoagulant therapy

Q: Would you test for D-Dimer?

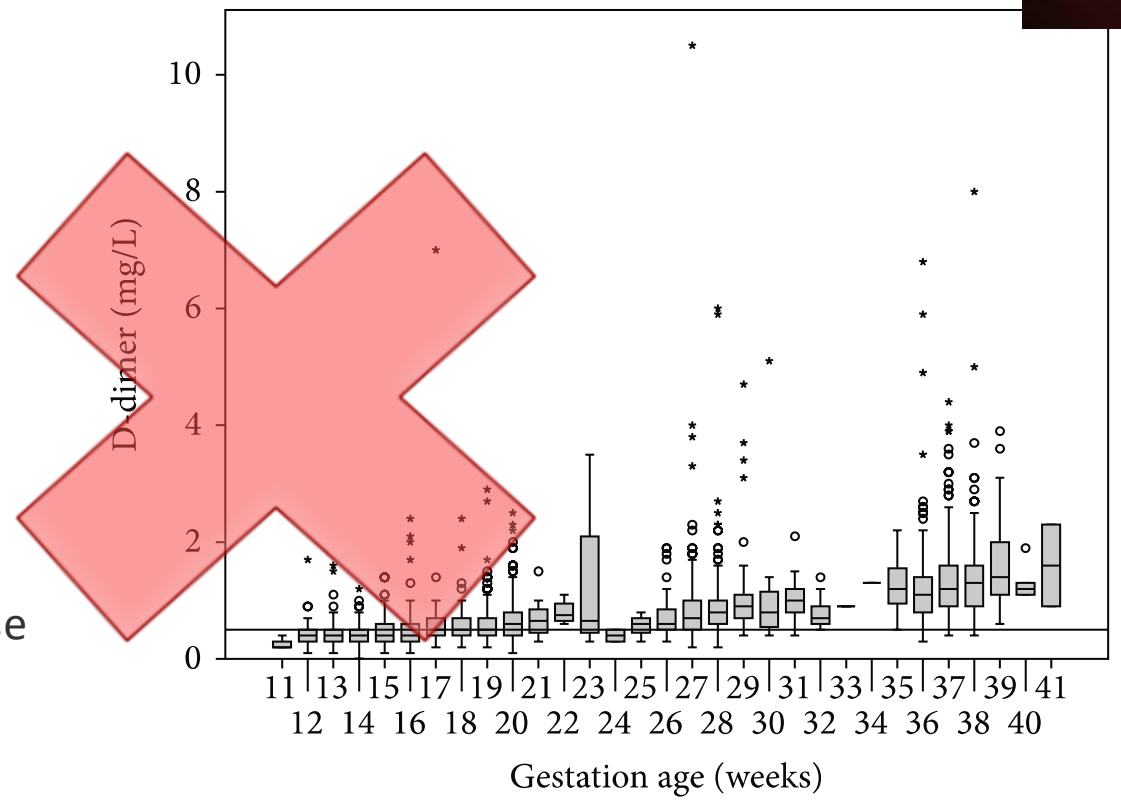
Q: Would you request a thrombophilia screen?

D-dimer testing in Pregnancy

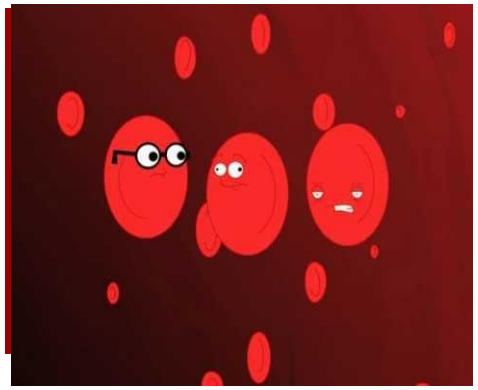


- Good negative predictive value: mostly positive in pregnancy

- Non-specific if positive:
  - Arterial thrombosis
  - VTE
  - DIC
  - Pregnancy
  - Infection/inflammation
  - Surgery/trauma
  - Severe liver/renal disease
  - Malignancy
  - Venous malformations



Thrombophilia Screen



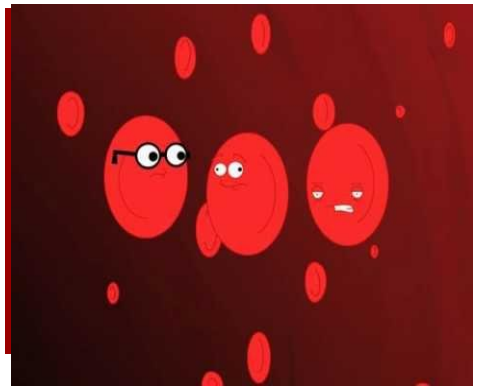
Inherited thrombophilia screen

- Unlikely to change management for patient - Generally I DO NOT go a screen
- Consider if:
  - strong family history. +++
  - history of recurrent VTE
  - VTE in usual sites
- FVL and PTG can be tested anytime
- Protein C, S, Antithrombin:
  - DO NOT test during acute thrombosis/during anticoagulation (falsely low)
  - DO NOT test in pregnancy (Protein C and S physiologically lower)

Acquired Thrombophilia screen

- Generally tested in all VTE patients[10]
- Antiphospholipid antibodies (anticardiolipin AB, B2 Glycoprotein)
- LAC

Imaging in pregnancy



- V/Q scan: slight increased risk of childhood cancer to foetus[4] (0.2% - 0.21%)
- CTPA scan: slight increase risk of breast cancer to proliferating breast tissue (increases lifetime risk 13.6% above background risk (0.1%); absolute risk 0.2%)[13, 14]

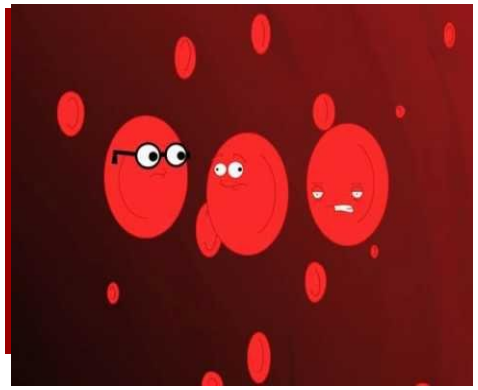
Either scenario:

Absolute risk to foetus and breast tissue very small

Benefits of the scans far outweigh any risk to her or her baby

Due to logistics/staff availability
Within Hours - generally VQ
After Hours. - generally CTPA.

Treatment of VTE in Pregnancy



- Which agent?
- What Dosing Regimen?
- How Long?
- Management issues around delivery….
- Doctor, will this affect my baby?

Anticoagulants in pregnancy

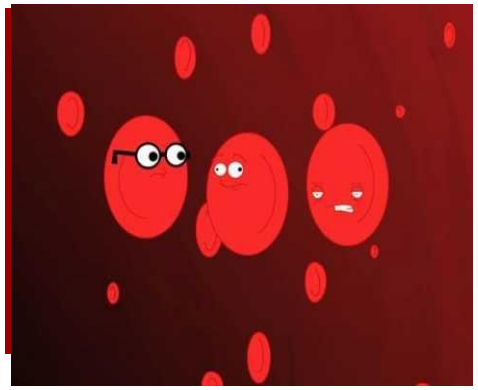
- Warfarin is CONTRAINDICATED in pregnancy
  - 1st trimester: nasal hypoplasia, stippling of bone, optic atrophy, mental retardation, cleft lip, cleft palate, cataracts, microopthalmia
  - Acceptable with breastfeeding

- DOACS are CONTRAINDICATED in pregnancy and breastfeeding

Heparins

- Both UFH and LMWH appear safe
- LMWH: Easier administration/predictable pharmacokinetics
- Heparins do not cross placenta and do not enter breast milk

Recommendations



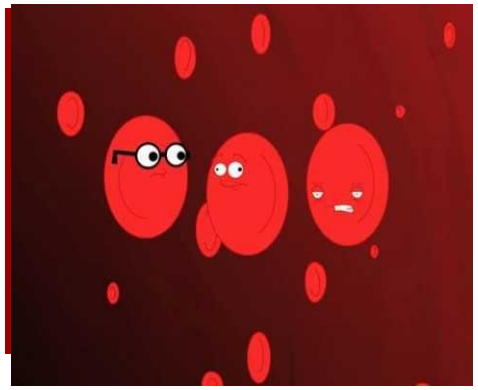
- **Therapeutic anticoagulation with LMWH is recommended in ALL pregnant patients with acute VTE**
  - Enoxaparin Bd dosing (1mg/kg) vs daily dosing (1.5mg/kg)
  - Insufficient evidence to favour one dose regimen over the other

- **Duration:**

- **Acute DVT and/or PE requires therapeutic anticoagulation for 3-6 months or until 6 weeks post-partum (whichever is later)**

- Isolated below knee DVT – may consider dropping to prophylactic dose after minimum 3 months therapeutic anticoagulation if DVT has completely cleared

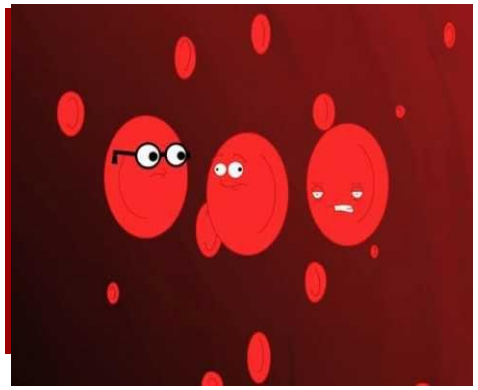
Treatment of PE in Pregnancy



- **Haemodynamically Stable** – Treat as for DVT;
  - Enoxaparin (bd dose preferable initially) for 6 months until 6 weeks postpartum (which ever is later)

- **Massive PE with cardiovascular compromise**
  - Urgent haematology, ICU, Obstetric consult
  - TTE
- +/- catheter directed thrombolysis/thrombectomy
- Systemic thrombolysis
  - High risk procedure
  - Only consider for women with life or limb-threatening complications of acute VTE
  - Maternal mortality rate 1.2%, bleeding rate 8.1%, foetal loss rate 5.8%[4].

Thromboprophylaxis in pregnancy and postpartum?



Minefield!

Thrombophilia

High risk

- Antiphospholipid Syndrome
- Antithrombin deficiency
- Homozygous Factor V leiden mutation
- Compound Heterozygote for FVL and PGM
- Protein C deficiency
- Protein S deficiency

Low Risk

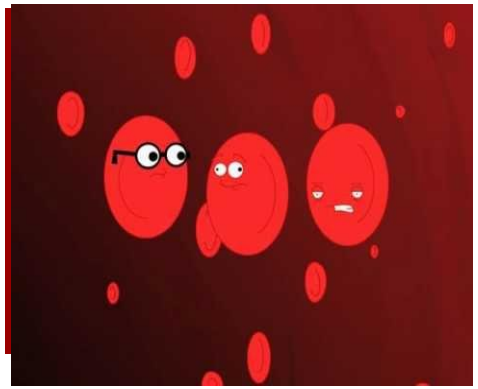
- Heterozygous FVL mutation
- Heterozygous PGM

Pre-Pregnancy risk factors

- Personal history of VTE
- Family history VTE (1st degree)
- Ovarian hyperstimulation syndrome
- Smoking
- Pre existing medical history

Antenatal risk factors

- Maternal age > 35 years
- Assisted reproduction
- Preterm birth
- Hypertensive history
- Obesity BMI > 30
- Multiparity (>3)
- Gross varicose veins
- Immobility
- Hyperemesis
- Sepsis
- C section
- PPH > 1L



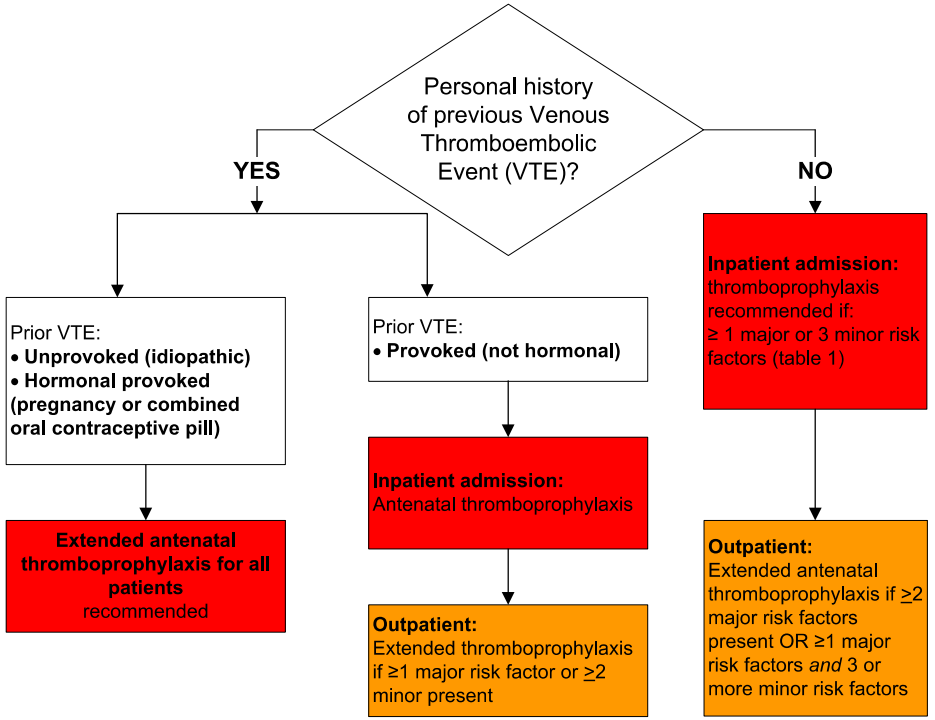


Table 1: Risk factors

Major
Body mass index ≥30 kg/m^2
Family history of VTE#
Preeclampsia
Known *significant* thrombophilia (table 2)
Active medical illness eg malignancy, nephrotic syndrome, pneumonia*

Minor
Maternal age ≥35 years
Immobilisation*
Smoker
Known *weak* thrombophilia (table 2)
Severe varicose veins
Multiple pregnancy
Severe hyperemesis
Parity (≥3)

* *eg bed rest or plaster of paris cast*
\# *event confirmed on imaging in a first degree relative*

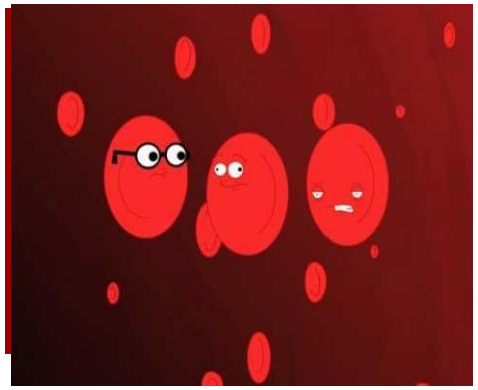
Table 2: Hereditary thrombophilia

Significant
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Homozygous factor V Leiden
Combined hereditary defects

Weak
Heterozygous factor V Leiden
Heterozygous G20210A prothrombin mutation

* Flowchart does NOT apply to women with antithrombin deficiency, antiphospholipid syndrome, multiple prior VTE on long term warfarin or prosthetic heart valve(s). *Such women should be discussed with an obstetric physician or haematologist*

When to refer to Haematology?



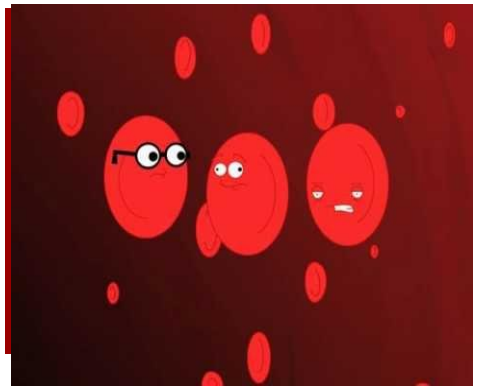
VTE Risk Assessment

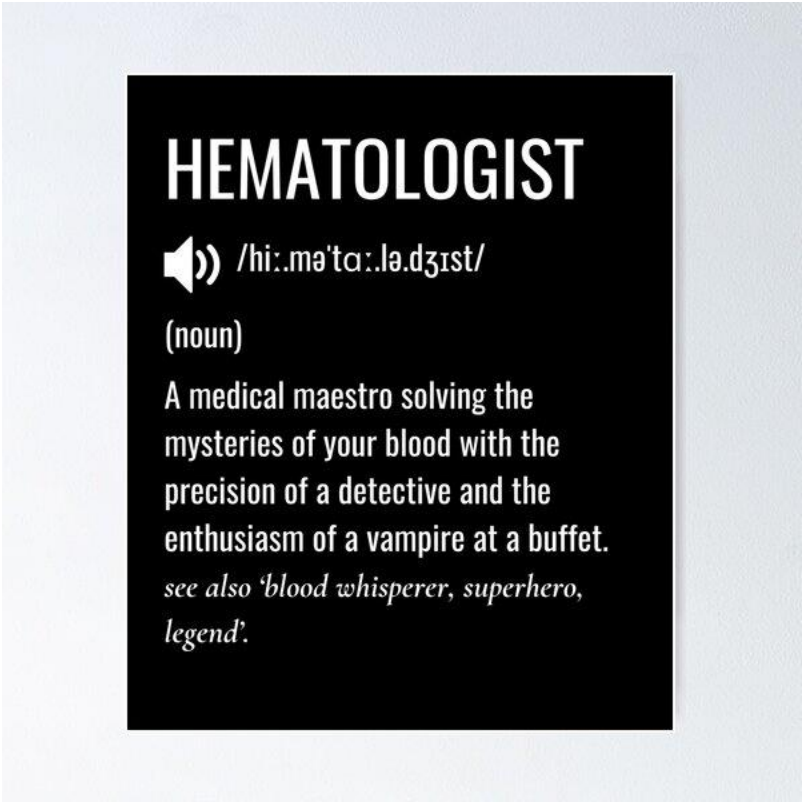
- All antenatal women require a VTE risk assessment at their first booking visit/consultation and at each antenatal inpatient admission (not including day admissions)

- Haematology Review is recommended :
  - Patients on anticoagulation prior to pregnancy
  - for all antenatal patients with a personal history of thromboembolism
  - high-risk cases or patients with multiple VTE Risk Factors
  - when there is any doubt about the correct management.
  - Any new VTE in pregnancy

- A postpartum VTE risk assessment is a mandatory requirement and must be performed in a timely manner post delivery

If in doubt, please call your friendly haematologist!





Questions?

HealthPathways Melbourne Overview

Shared Maternity Care Collaborative Workshops

15 October 2024

Pathways are written by GP clinical editors with support from local GPs, hospital-based specialists and other subject matter experts

- clear and concise, evidence-based medical advice
- Reduce variation in care
- how to refer to the most appropriate hospital, community health service or allied health provider.
- what services are available to my patients

HealthPathways – Shared Maternity Care

HealthPathways Melbourne

Relevant pathways:

- Antenatal - Second and Third Trimester Care
- Decreased Fetal Movements
- Hypertension in Pregnancy and Postpartum
- Sexual Health
- Skin Conditions (Rash and Itch) in Pregnancy
- UTI and Asymptomatic Bacteriuria in Pregnancy
- Varicella and Pregnancy

CPD Hours for HealthPathways Use

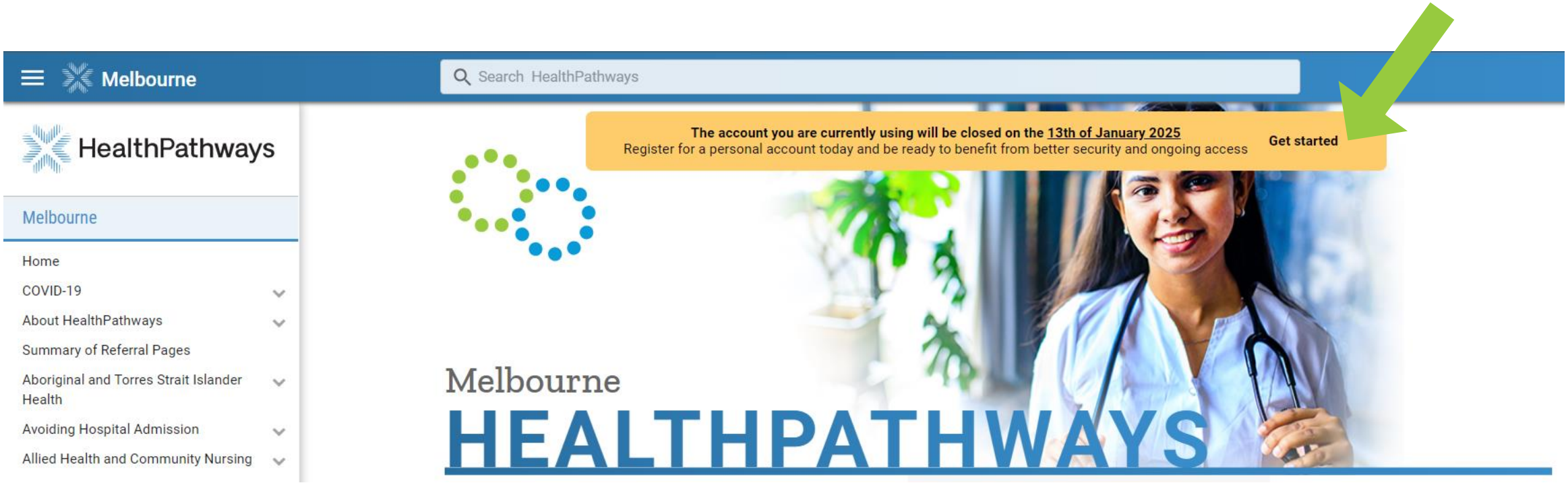
Referral pathways:

- Pregnancy Medical Conditions
- Acute Obstetric Referral or Admission (Same-day)
- Non-acute Obstetric Referral (> 24 hours)
- Early Pregnancy Assessment Service (EPAS)
- Pregnancy Booking
- Acute Infectious Diseases Referral (Same-day)
- Non-acute Infectious Diseases Referral (> 24 hours)
- Sexual Health Referrals
- Non-acute Sexual Health Referral (> 24 hours)
- Sexual Health Advice

Accessing HealthPathways

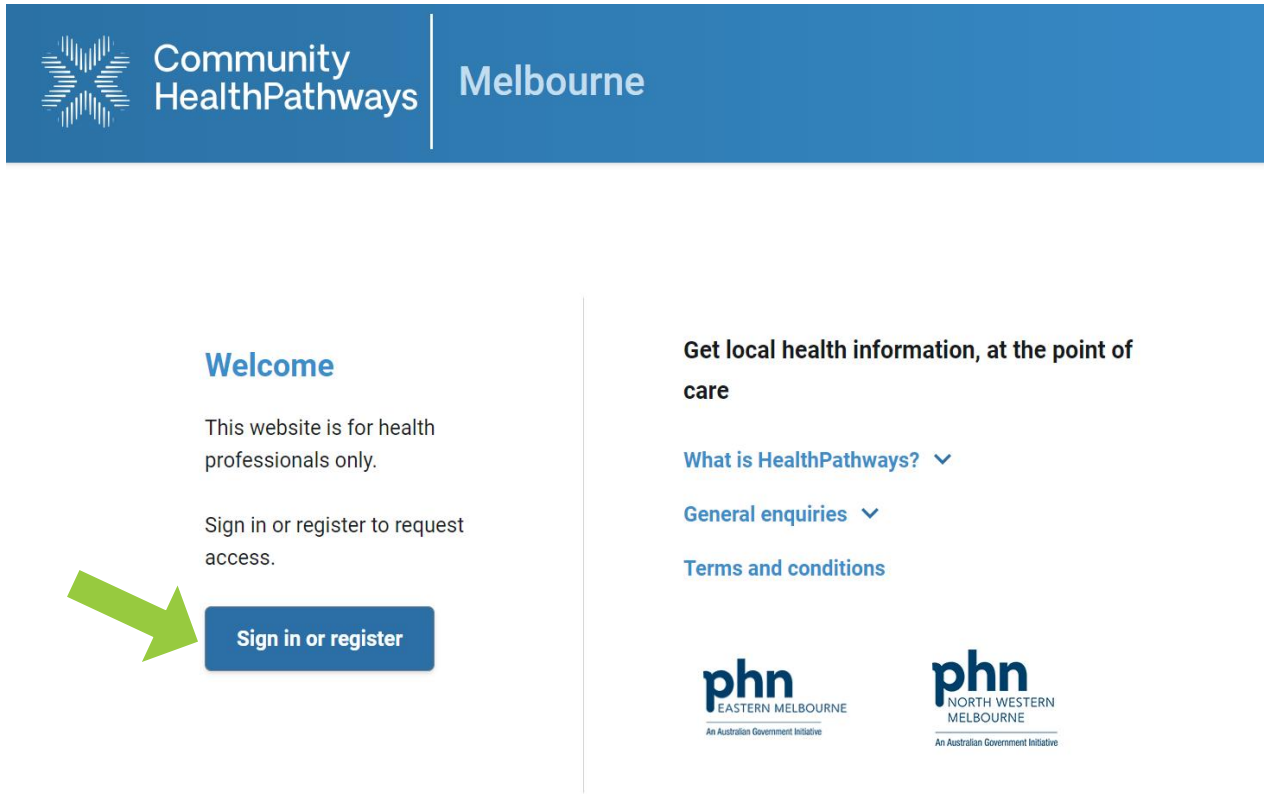
From 30 September 2024, eligible users can sign sign-up for your individual HealthPathways Account.

For existing users, once logged in, you will see a banner at the top of the screen inviting you to start the process. Simply click on the banner to start creating your individual HealthPathways account.



Accessing HealthPathways

For new users, go to melbourne.healthpathways.org.au or scan the QR code to register.



Questions? Contact the team on:

info@healthpathwaysmelbourne.org.au

Health Service and Partner Updates

Shared Maternity Care Workshop 1 (8 Oct 2024)

You can access the recording to the first Shared Maternity Care Workshop online

- **Third Trimester Issues**
- **Perinatal Infections**

https://nwmphn.org.au/resource/shared-maternity-care-workshop-1-third-trimester-issues-and-infectious-diseases-in-pregnancy-8-october-2024/

Mercy Health Update

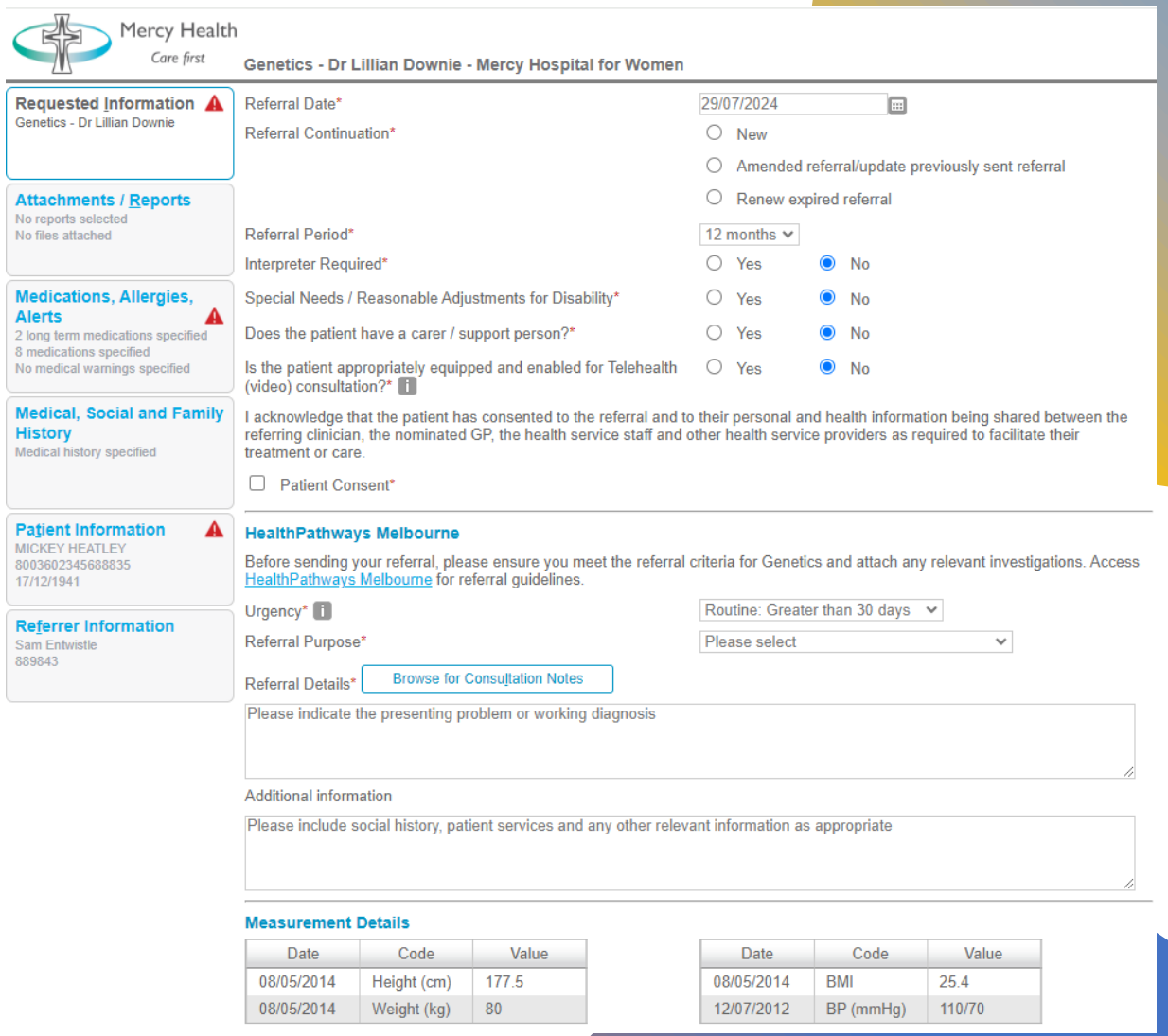
Mercy Health
Care first

Exciting things are coming to Mercy Hospital for Women!
Our first **GP speed dating event is** coming soon and the commencement of our newly established **Primary Care Liaison Advisory committee** EoI will be available in the coming weeks**.**

Stay up to date with all to come in Werribee Mercy Hospital.
You will receive information about the ED expansion, clinical information and education possibilities via the newsletter.

Please ensure you have signed up to our Primary Care Liaison **newsletter** via the Mercy Health, Primary Care Liaison webpage.

Mercy Health's preferred referral method for its Outpatient Specialist Clinics is via eReferrals, HealthLink SmartForms.
For more information visit our HealthLink eReferral infomation website


Mercy Health
Care first

Genetics - Dr Lillian Downie - Mercy Hospital for Women

Requested Information
Genetics - Dr Lillian Downie

Attachments / Reports
No reports selected
No files attached

Medications, Allergies, Alerts
2 long term medications specified
8 medications specified
No medical warnings specified

Medical, Social and Family History
Medical history specified

Patient Information
MICKEY HEATLEY
8003602345688835
17/12/1941

Referrer Information
Sam Entwistle
889843

Referral Date* 29/07/2024
Referral Continuation* New / Amended referral/update previously sent referral / Renew expired referral
Referral Period* 12 months
Interpreter Required* Yes / No
Special Needs / Reasonable Adjustments for Disability* Yes / No
Does the patient have a carer / support person?* Yes / No
Is the patient appropriately equipped and enabled for Telehealth (video) consultation?* Yes / No

I acknowledge that the patient has consented to the referral and to their personal and health information being shared between the referring clinician, the nominated GP, the health service staff and other health service providers as required to facilitate their treatment or care.

Patient Consent*

HealthPathways Melbourne

Before sending your referral, please ensure you meet the referral criteria for Genetics and attach any relevant investigations. Access HealthPathways Melbourne for referral guidelines.

Urgency* Routine: Greater than 30 days
Referral Purpose* Please select
Referral Details* Browse for Consultation Notes

Please indicate the presenting problem or working diagnosis

Additional information

Please include social history, patient services and any other relevant information as appropriate

Measurement Details

Date	Code	Value
08/05/2014	Height (cm)	177.5
08/05/2014	Weight (kg)	80

Date	Code	Value
08/05/2014	BMI	25.4
12/07/2012	BP (mmHg)	110/70

Western Health

Western Health Transition to HealthLink

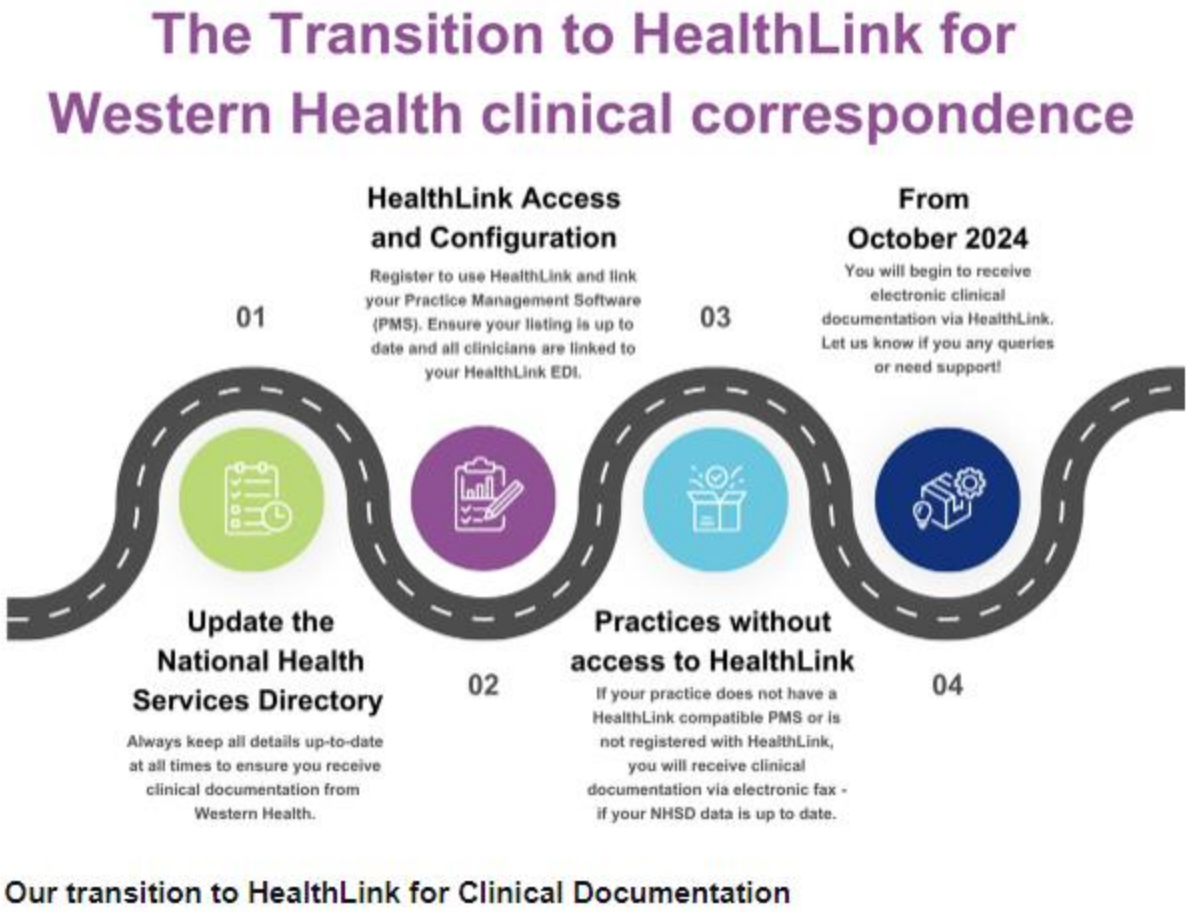
- Western Health (WH) is transitioning to HealthLink as our sole Secure Messaging Delivery (SMD) provider for clinical documentation.
- Starting in October 2024, all clinical correspondence for GPs will be sent through HealthLink, and our previous SMD provider, PulseNet, will be decommissioned.
- Our goal is to move all clinical correspondence for GPs to HealthLink by the end of 2024.
- For support with transitioning to HealthLink, please reach out to the Western Health GP Integration Unit:

gp@wh.org.au

or 03 8345 1735.

- For more information, visit https://www.westernhealth.org.au/HealthProfessionals/ForGPs

Western Health Transition to HealthLink



Royal Women's Hospital

Public Fertility Care & RACGP Victoria webinar

Causes of fertility, how to investigate, when to refer

Thursday 24 October 2024, 6 - 7pm

https://www.thewomens.org.au/health-professionals/for-gps/gp-cpd-events

Subscribe to our quarterly GP News for updates

https://www.thewomens.org.au/health-professionals/for-gps/gp-news/

the women's
the royal women's hospital

phn
NORTH WESTERN MELBOURNE
An Australian Government Initiative

Perinatal mental health and psychotropic medicines in pregnancy

Tuesday 1 October 2024

Email: gp.liaison@thewomens.org.au

The content in this session is valid at date of presentation

https://www.youtube.com/watch?v=Z2NqxA2SBSs

PANDA – Perinatal Anxiety and Depression Australia

We provide Australia's only National Perinatal Mental Health Helpline, plus a range of digital supports for expecting and new parents, and the people who care for them.

PANDA National Helpline

1300 726 306
(weekdays 9am–7:30pm. Saturdays 9am-4pm AEST)

Free phone-based support for perinatal mental health and emotional wellbeing challenges

No Medicare required

Interpreters available

Follow-up support

PANDA
Perinatal Anxiety & Depression Australia

PANDA Programs & Services

We provide counselling, peer support and care coordination

Intensive Care & Counselling (funded in VIC & QLD)

Free secondary consultation service for healthcare providers

Resources to share with families in your care

Download or order free hardcopies of PANDA posters, factsheets, brochures via our website

Resources for First Nations families

Translated resources in over 40 community languages

panda.org.au

Online referral form

Access to free courses on PANDA Learning Hub

PANDA Mental Health Checklists

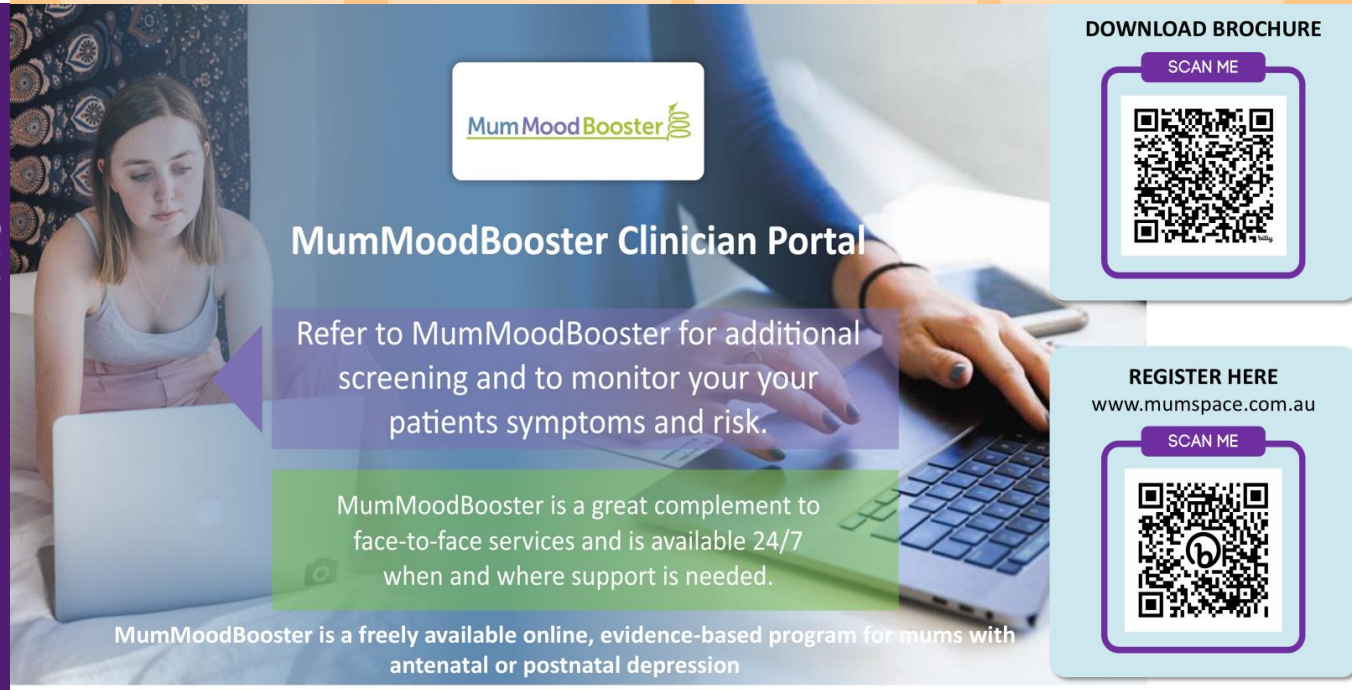
Real life stories

Resources for self-support, carers and healthcare providers

Survive and Thrive podcast

Psychotropic Prescribing in Perinatal Period

Dr Charles Su
CL Consultant Psychiatrist
Charles.su@thewomens.org.au



Increasing access to abortion health care in north east Melbourne

- A joint initiative to increase access to early medical abortion (EMA) in primary care settings in north east metro Melbourne
- Identified need for improved access in Hume, Whittlesea and Yarra Ranges LGAs
- Healthcare providers are encouraged to consider becoming a publicly list EMA provider, and/or providing patients with information other local services

To discuss becoming a listed EMA provider, or for further information, use the contact request form here

Project partners:

North Eastern Public Health Unit (NEPHU)
North Western Melbourne Primary Health Network
Women's Health in the North
Women's Health East
1800 My Options

Further information:

https://nephu.org.au/news-and-events/ema-access

https://www.1800myoptions.org.au/for-professionals/become-an-mtop-provider/

NEPHU NORTH EASTERN PUBLIC HEALTH UNIT

Session Conclusion

We value your feedback, let us know your thoughts.

Scan this QR code

You will receive a post session email within a week which will include slides and resources discussed during this session.

Attendance certificate will be received within 4-6 weeks.

To attend further education sessions, visit,

https://nwmphn.org.au/resources-events/events/

https://nwmphn.org.au/resources-events/resources/