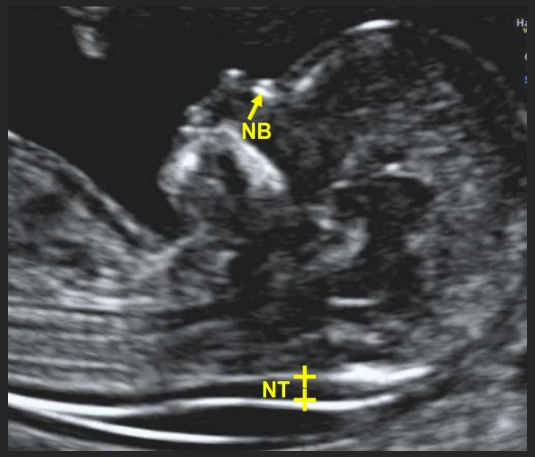


First Trimester Screening & Pregnancy Management

Shireen Meher
Professor of Maternal Fetal Medicine
University of Sydney Nepean Clinical School
Nepean Hospital

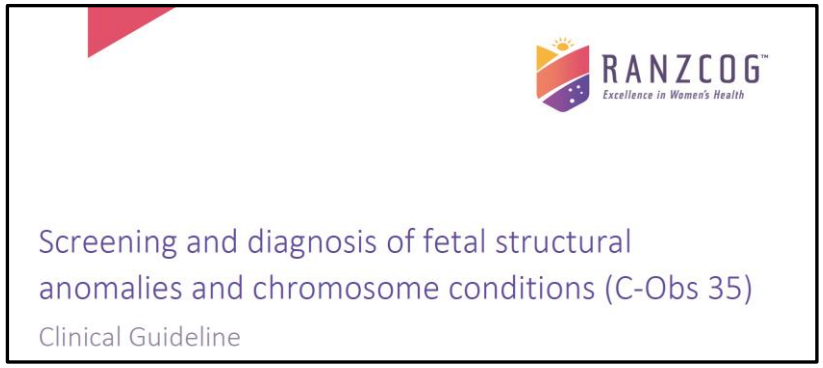
Aim

- Screening tests
  - Chromosomal abnormalities
    - Combined First Trimester Screening (cFTS)
    - Non-invasive Prenatal Testing (NIPT)
  - Pre-eclampsia combined first trimester screening
- Background / rationale
- Pregnancy management
- Costs
- Services at Nepean Hospital

Background: First Trimester Aneuploidy Screening

- Aim: to identify pregnancies at high risk of Trisomies 21, 18, and 13
- Rationale
  - 1-2 % of pregnancies
  - Most common cause of
    - 1st trimester pregnancy loss
    - structural anomalies
    - neurodevelopmental impairment in infants
  - Account for 58% of all major chromosomal abnormalities
  - Allows timely counselling about risks / options
  - Additional diagnostic investigations
  - Supports patient choices and decisions
  - Involve multidisciplinary team
  - Preparation for management at birth

National Guidelines



Good Practice Point 1

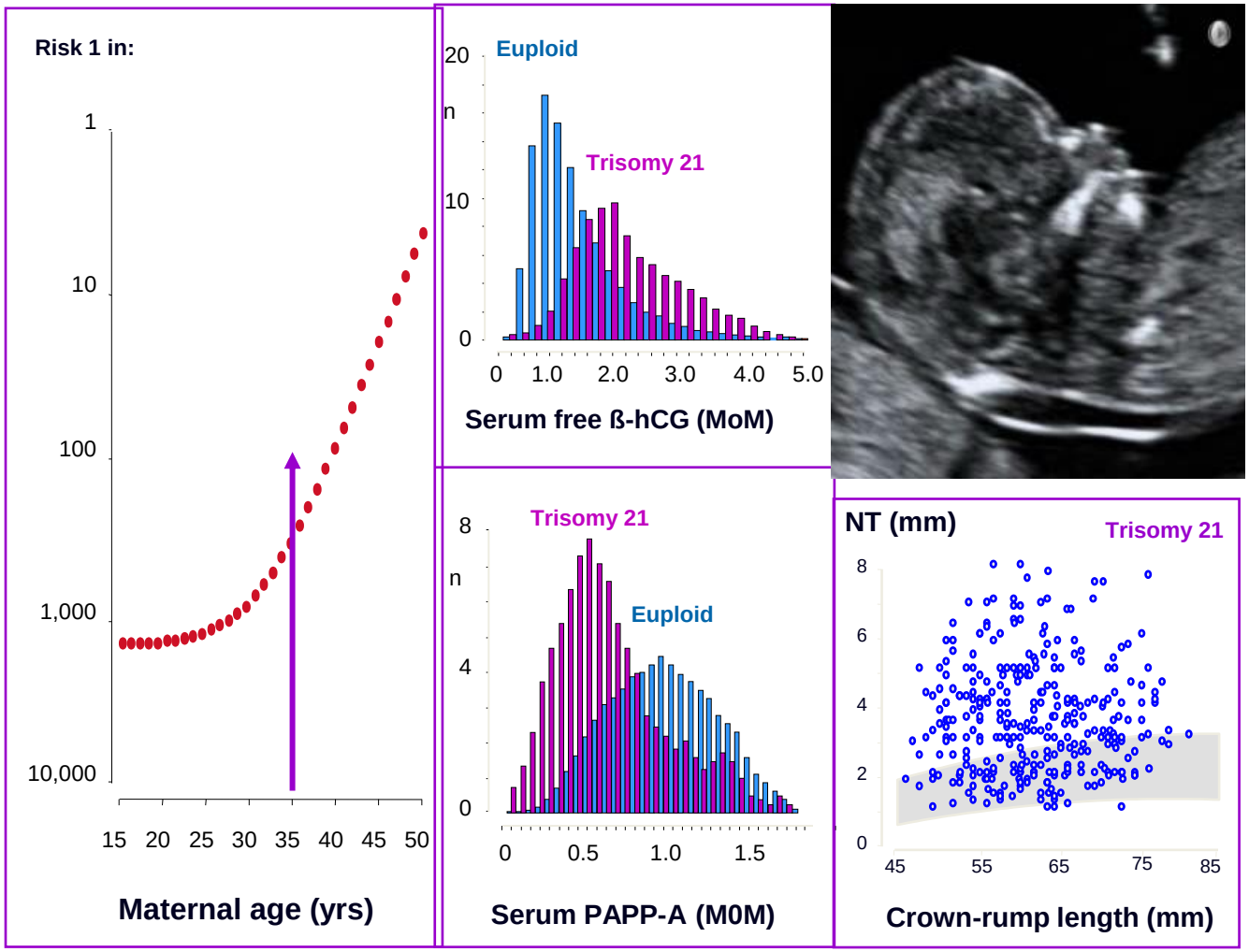
GPP: The GDG recommends that all pregnant women should be provided with balanced information and have timely access to screening tests for fetal chromosome and structural conditions. Prenatal screening options should be discussed and offered in the first trimester whenever possible.

Primary screening for Trisomy 21, 18, and 13 before 14 weeks gestation

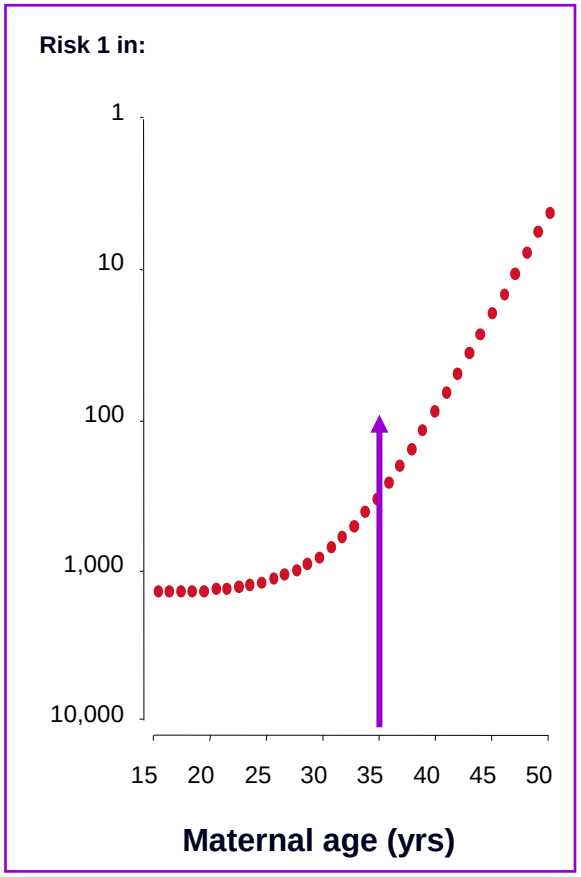
Pre-test counselling

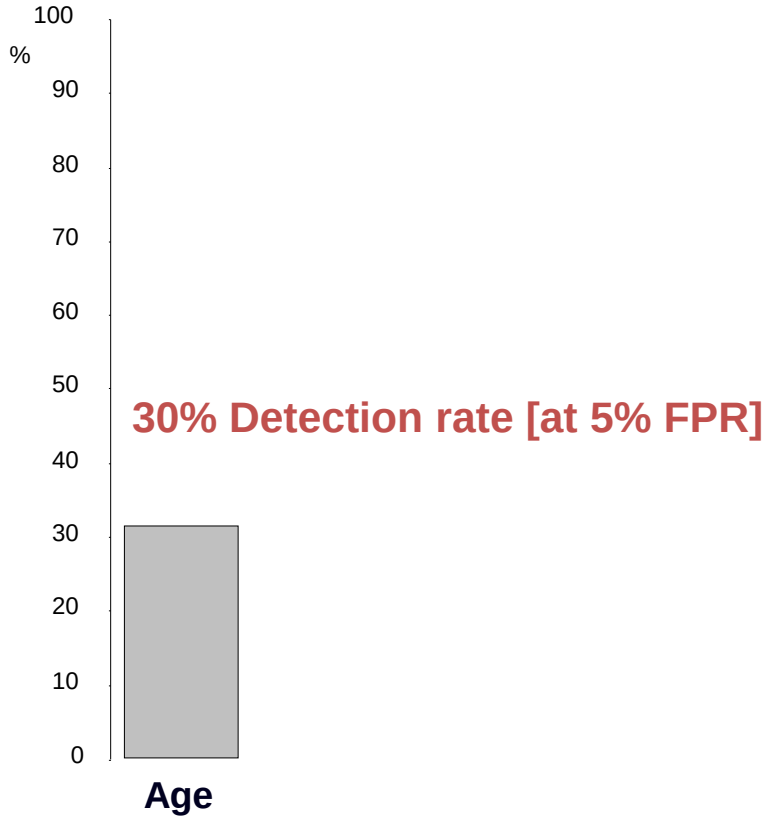
- Recognise a woman's preferences and values
- Difference between screening and diagnostic testing
- Benefits and limitations of tests
- Conditions screened for and those not assessed
- Patient-specific factors that impact choice of a test: age, family hx, NT >3.5 mm
- Potential outcomes and options for further testing
- How and when test results will be communicated
- Potential costs of testing /Medicare-rebated.

Foundations of combined First Trimester Screening



cFTS: maternal age

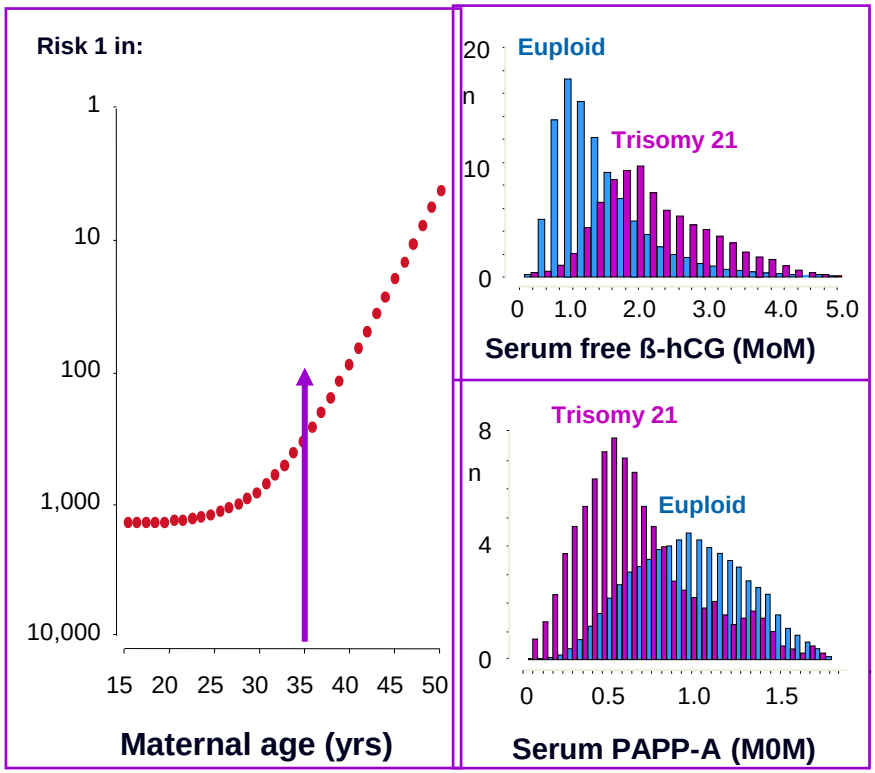


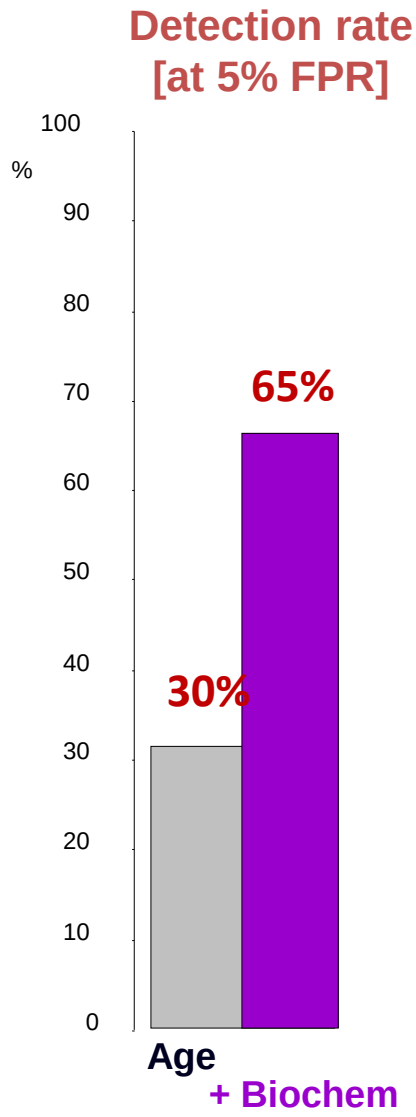


Current screening strategy: maternal age is used to calculate a-priori risk (along with history of a previous pregnancy affected by trisomy 21)

CFTS: biochemical markers

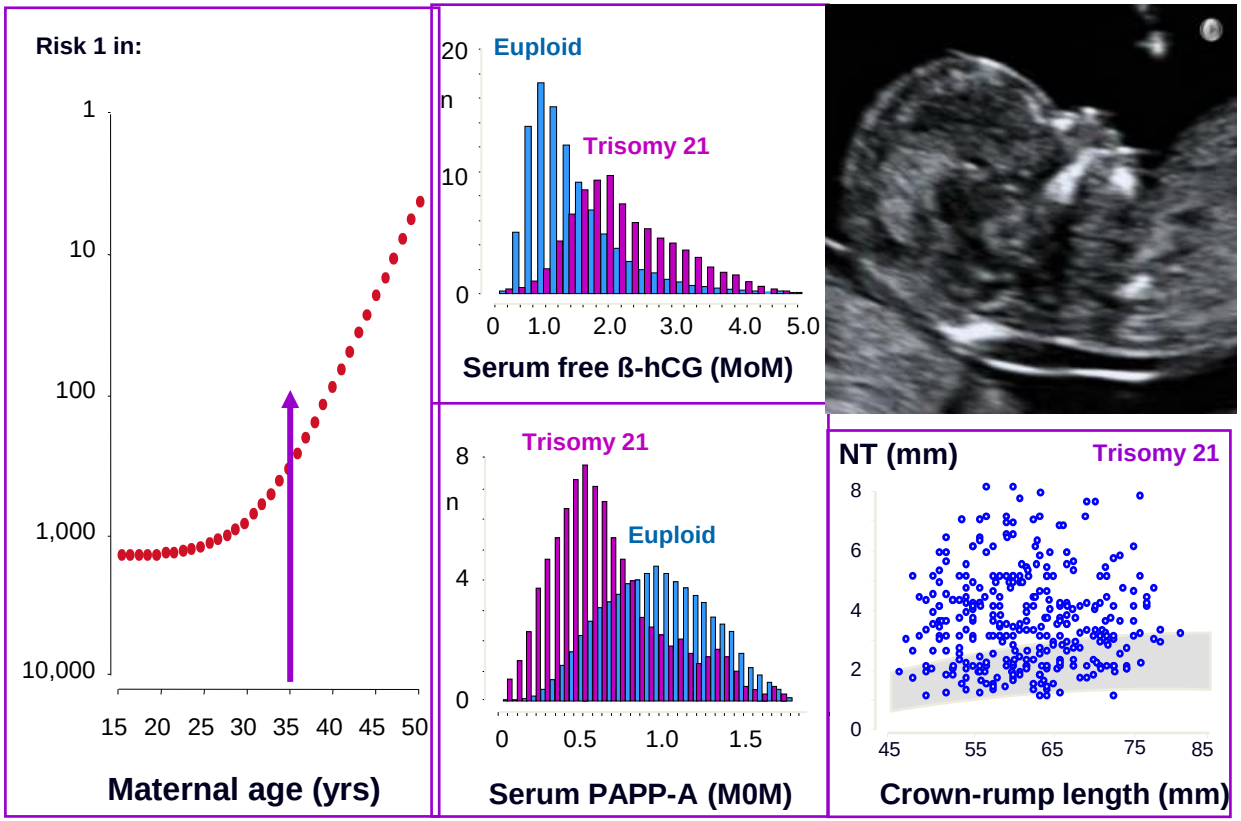
- Blood test for biochemical markers
  - Free beta-human chorionic gonadotropin (ß-hCG)
  - Pregnancy associated plasma protein-A (PAPP-A)
  - 10^{+0} to 13^{+6} weeks gestation

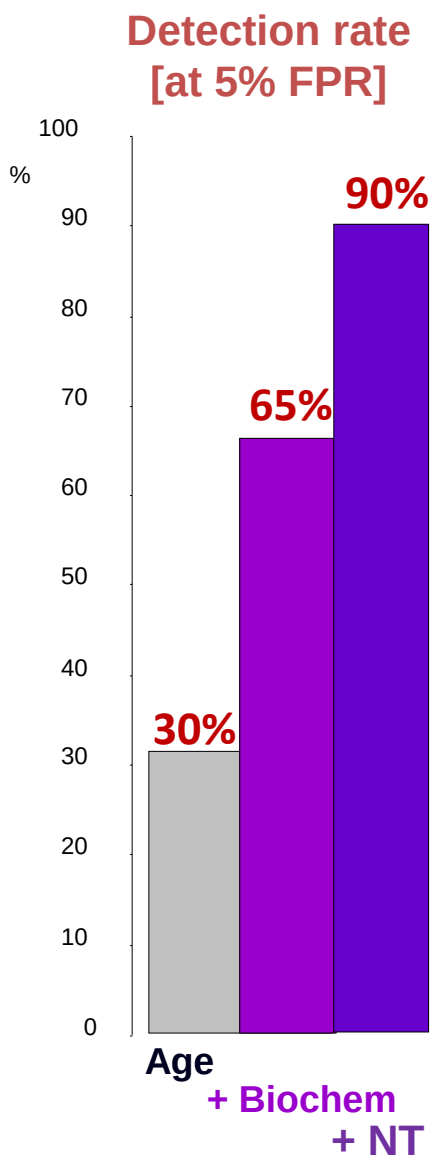




cFTS: nuchal translucency

- Ultrasound marker: Nuchal Translucency (NT)
  - Fetus with a crown-rump length (CRL) of 45–84 mm
  - 11^{+0} to 13^{+6} weeks gestation





First Trimester (NT) Scan

- Also of value for
  - confirming viability
  - accurate dating of pregnancy
  - identification of multiple pregnancies
  - identification of major fetal structural abnormalities
  - assessing maternal ovaries / pelvic structures
  - identification of risks for adverse pregnancy outcomes such as preeclampsia (uterine artery doppler)

Interpretation of cFTS results

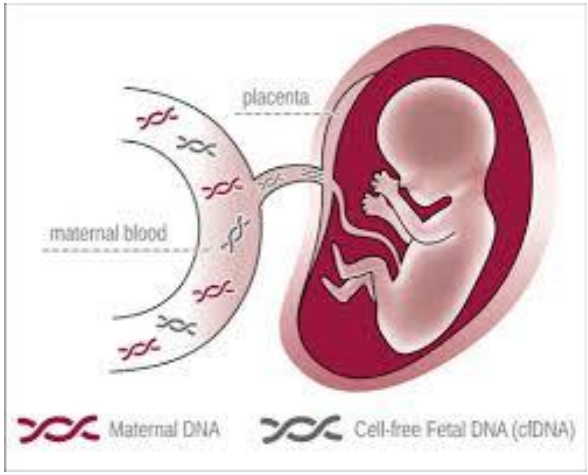
- Markers converted into multiple of medians (MoMs) for risk calculation
  - Control for variation with gestational age and maternal factors e.g., weight, ethnicity, smoking, etc)
  - Standardisation across labs
  - Easier to interpret

- ß-hCG level increases in T21, decrease in T18 and T13
- PAPP-A levels decrease in T21, T18 and T13 (more in T18)

- High risk result: ≥ 1:300
- Intermediate risk result: 1:301 to 1:1000
- Low risk: <1:1000

Non-invasive Prenatal Testing (NIPT)

- Around 90% of cell-free DNA fragments are maternal in origin, but 10% are placental and identified as the fetal fraction.
- Genomic analysis of fetal fragments of cell free DNA in maternal plasma.
- Offer from 10 weeks – no upper gestational age limit
- All currently available assays include screening for trisomies 13,18 and 21 and sex chromosome aneuploidies
- Commercial providers offer various options for extended testing: clinicians must be aware of how these perform if they are offering or referring for testing.
- Ultrasound not included – arrange baseline scan prior to NIPT



NIPT detection rates

Highest level of screening efficacy

	Detection Rate	FPR
Trisomy 21	99.7% (CI: 99.1 – 99.9)	0.04%
Trisomy 18	98.2% (CI: 95.5 – 99.2)	0.05%
Trisomy 13	99.0% (CI: 65.8 – 99.9)	0.04%

Gil *et al.* Meta-analysis UOG 2017

NIPT detection rates: sex chromosomal abnormalities (SCA)

	Pooled Detection Rate	Specificity
SCA overall	94.1% (95% CI: 90.8 – 96.3)	99.5% (90.7 to 98.9)

SCA	Positive Predictive Value (95% CI)
Turner syndrome - 45X0	32.0% (27.0 – 37.3)
Klinefelter syndrome – 47 XXY	67.7% (62.5 – 72.5)
Triple X syndrome: 47 XXX	57.5% (51.7 – 63.0)
Jacob's syndrome 47 XYY	70.9% (63.9 – 77.1)

Bussolaro et al,. AJOG 2023

NIPT: extended panel for microdeletions, microduplications and CNVs

	Positive Predictive Value (95% CI)
Di George 22q.11.2 deletion	15% - 93%
Prader–Willi, Angelman+/- Cri du chat microdeletion syndromes	5% - 75%
Genome wide microdeletion and microduplication syndromes: CNVs >10 Mb	32%
Genome wide microdeletion and microduplication syndromes: CNVs <10 Mb	19%

- Rare disorders: clinical validity difficult to establish as number of samples from affected pregnancies is limited
- Wide variation with techniques / algorithms used
- Not sufficiently accurate to be offered routinely: high risk of false positives

- Martin et al., Clin Gen 2018
- Liang et al, Genet Med 2019

NIPT: Limitations

- Limited to T21, T18, T13, sex aneuploidy
- Not diagnostic
- May not be the most appropriate test in some clinical situations:
  - Increased risk of aneuploidies other than T21, T18, T18
    - The nuchal translucency measures ≥ 3.5mm
    - Structural anomaly detected on ultrasound
  - There is repeated NIPT screening failure
  - Higher risk of false negatives or positives / test failure (T18, XO, mosaicism)
    - The free β- HCG greater than ≥ 5.0 MoM or < 0.2 MoM
    - The PAPP-A measures < 0.2 MoM

NIPT: Results

- High risk result
- Low risk result
- Test failure or ‘no call’ result - 1-6%
  - Usually due to low fetal fraction (<10 weeks gestation)
  - More likely in some aneuploidies (T18, T13), high BMI
  - Management options
    - Repeat test (no extra cost)
    - Alternative screening tests e.g, cFTS
    - Diagnostic test

Screening in Twins

- Combined First Trimester Screening
  - Dichorionic twins: risk per fetus
  - Monochorionic twins: risk per pregnancy (average risk)
  - Detection rate similar to singleton pregnancies: DR 87% for 5% FPR
  - More likely to be offered invasive procedure

- NIPT (less data)
  - Detection rate 99% for T21, 93% for T18 and 95% for T13,
  - False positive <0.2%
  - Failure rate higher: 2.9 to 9.4%
  - More accurate in MC vs DC twins
  - Cannot determine which fetus is affected / both affected

- Vanishing twin: high risk of false positives with NIPT

Management of high risk result: general principles

- Post-test counselling
  - Interpretation of results
  - Establish whether the woman wishes to proceed with any further testing: support autonomy in decision making
  - Discuss options for further testing: risks and benefits
  - Ensure other health professionals involved in managing the pregnancy are aware of results

- Referral to Fetal Medicine Specialists for counselling / diagnostic tests
  - Chorionic Villus Sampling (CVS)
    - 11 to 14 weeks gestation
    - Miscarriage risk: 0.2 to 2% (1:500)
  - Amniocentesis
    - 15 weeks onwards
    - Miscarriage risk: 0.1 to 1% (1:1000)

Management: High Risk Screening Result

- No further action: committed to pregnancy
- Diagnostic testing with amniocentesis or CVS: NIPT / cFTS result must be confirmed before offering termination of pregnancy
- For high risk cFTS result: contingent NIPT test

Contingent NIPT test

- NIPT may be offered after
  - high-risk result from cFTS
  - intermediate risk result (1:301 to 1:1000) – group with most false negative cFTS results

- Lower detection rate (89% - 100%) and higher false positive rate (0.3 to 1.4%) after high risk cFTS

- Not publicly funded in Australia

- Data from Victoria (2015)
  - 1% chose to have contingent NIPT
    - 22% for high risk CFTS
    - 20% for Intermediate result

Pre-eclampsia: why screen?

Affects 2-5% of pregnant women (4.3% in NSW)

15 Maternal deaths / year

1/3 of all severe maternal morbidity

1/4 of all maternal ICU admissions

- Eclamptic seizures
- Cerebrovascular accident
- Pulmonary oedema and ARDS
- Renal failure
- Liver failure (HELLP)
- DIC

Ongoing long-term risks

- Hypertension
- Ischaemic heart disease
- Cerebrovascular accidents

15% of all preterm births
15% of IUGR infants
5% of stillbirths

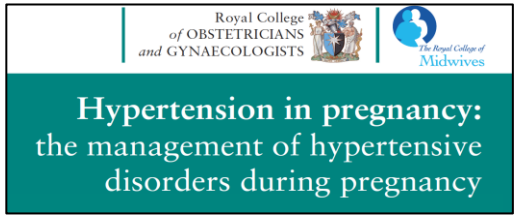
Ongoing long-term risks

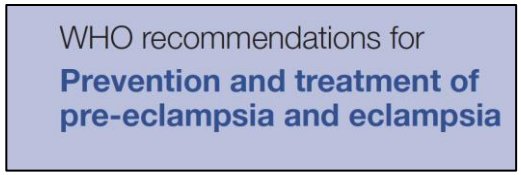
Developmental delay
Obesity
Hypertension
Cardiovascular disease / Metabolic syndrome

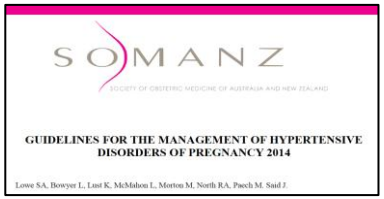
AIHW 2016; ANZNN Report 2016

Aim of First Trimester PET Screening

- Identify pregnancies at high risk of pre-eclampsia
  - Choose appropriate model of care / surveillance in pregnancy
  - Predict to prevent: aspirin







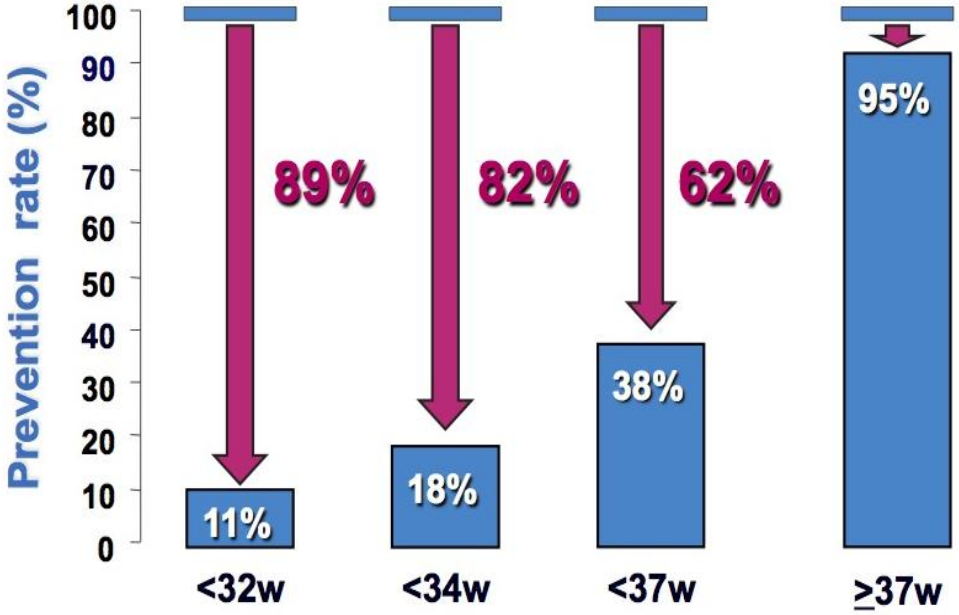
Low-dose aspirin is recommended for prevention of pre-eclampsia and its complications in women with risk factors

Why Screen: Available preventative intervention

The Fetal Medicine Foundation

ASPRE project

Prevention of preeclampsia



The NEW ENGLAND JOURNAL of MEDICINE

Rolnik DL, Wright D, Poon L, et al. Aspirin versus placebo in pregnancies at high risk of preterm preeclampsia. N Engl J Med 2017;377:613-22.

Screening for pre-eclampsia

NICE / ACOG /SOMANZ Guidelines

High risk factors
Previous pre-eclampsia/GH
Chronic hypertension
Renal disease
Diabetes
SLE/APS
Moderate risk factors
Nulliparity
Age ≥ 40 (≥35 in ACOG)
BMI ≥ 35 (≥30 in ACOG)
Multifetal pregnancy
Family history of pre-eclampsia
Interpregnancy interval >10 yrs
Black ethnicity / low income (ACOG)
IVF conception (ACOG)

Simple to implement

Combined First Trimester PET Screening

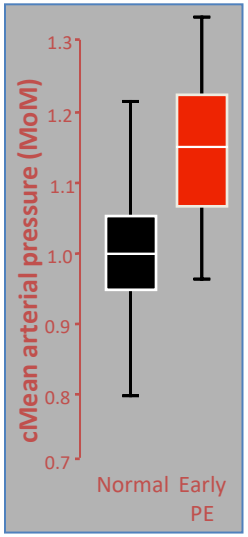
High risk factors
Maternal history
Biophysical markers (MAP, Uterine artery PI)
Biochemical markers (PLGF, PAPP-A)

Resources, training

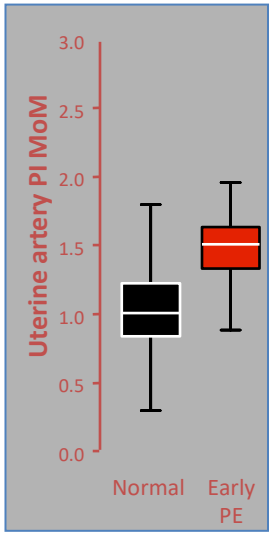
Additional tests not routinely done

Biophysical markers

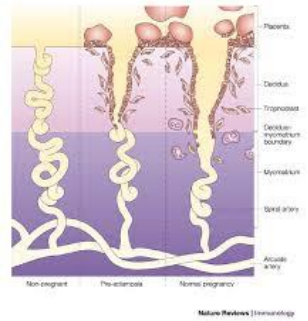
Mean Arterial Pressure (MAP) =
Diastolic Pressure + 1/3 (Systolic Pressure - Diastolic Pressure)



Uterine artery Pulsatility Index: requires training and expertise



Biochemical markers

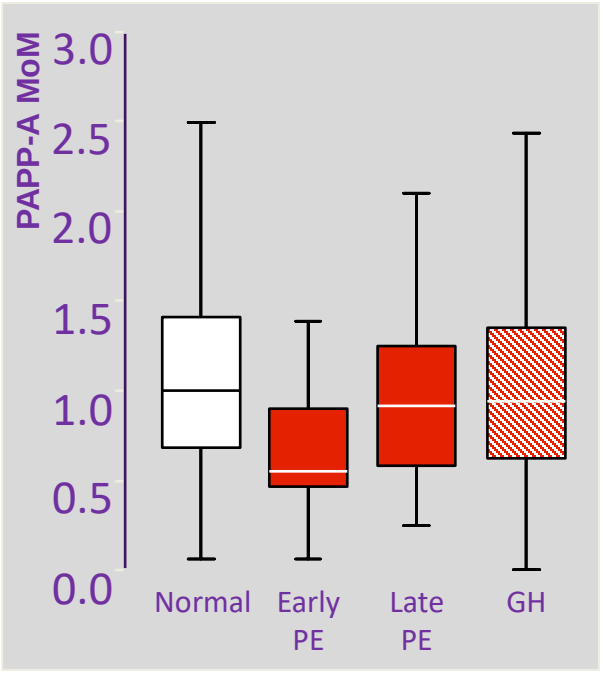


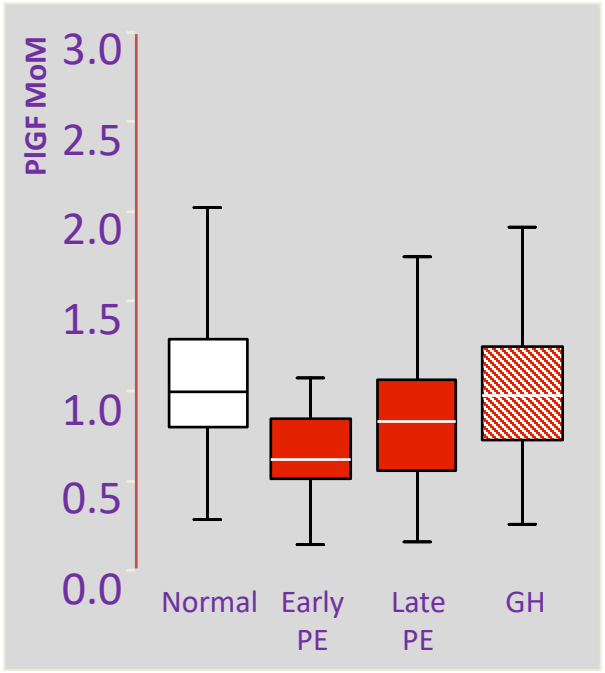
Placental dysfunction

Placental ischaemia

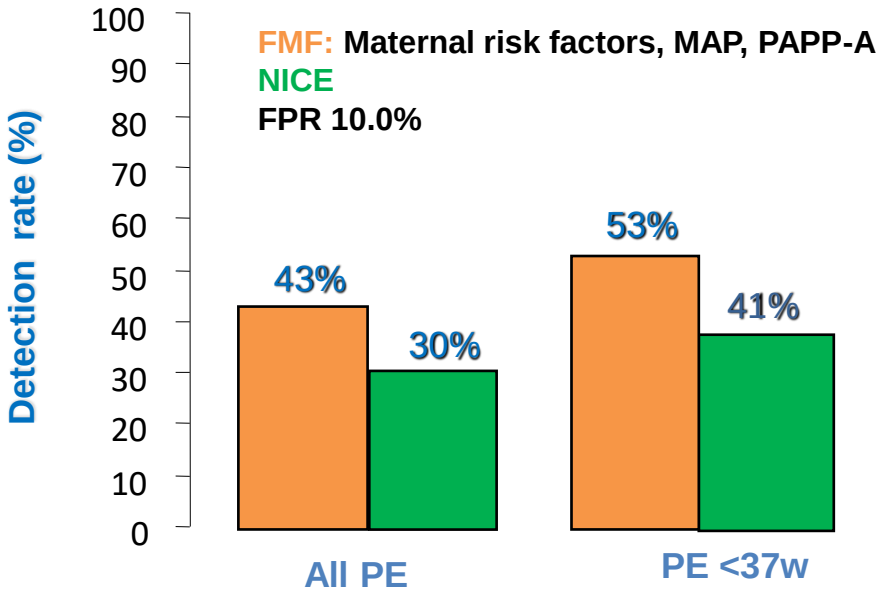
Oxidative stress

- ↓ Ut Art flow
- ↓ PaPP-A
- ↓ PlGF





NICE screening vs cFTS for PET



Detection rate for preterm PET for 10% FPR	
Mat factors + MAP + PAPP-A	53%
Mat factors + MAP + PLGF	69%
Maternal factors + MAP + PLGF + Ut A PI	82%

Improved detection rate for pre-eclampsia with biomarker screening

Tan et al, UOG 2018

National Guidelines

RANZCOG
Excellence in Women's Health

Category: Clinical Guideline

Early pregnancy screening and prevention of preterm preeclampsia and related complications

Recommendation 1	Evidence based recommendation

Strong: Offer routine screening in early pregnancy for preterm preeclampsia to all women.

Good Practice Point 1

GPP: In settings where the complete algorithm may not be feasible, consideration may be given to the use of some but not all components of the algorithm. Evidence suggests that any additional components to maternal history and BP are likely to improve the ability to detect women who will go on to develop preterm preeclampsia.

When screening for preterm preeclampsia, maternal risk factors and BP measurements are the minimum requirements to identify women at risk of developing preterm preeclampsia using the Fetal Medicine Foundation (FMF) algorithm (Available online - The Fetal Medicine Foundation).

- Cost-effective ($1.4 million, based on preterm PET cases prevented
- Roadblocks:
  - resources / expertise
  - pre-term PET less common (0.4%)
  - Not publicly funded

SOMANZ

Hypertension in Pregnancy Guideline

2023

Recommendations

2.1 The use of maternal risk factors (maternal characteristics, medical and obstetric history) to screen all pregnancies for risk of preeclampsia is strongly recommended (Table 2.1). (1A)

2.2 The use of a combined first trimester screen (combined maternal features, biomarkers and sonography) to identify women at risk of developing preeclampsia is conditionally recommended (2B) based on local availability and access to the required resources.

Results: interpretation and management

- Test before 16 weeks gestation, ideally 11^{+0} to 14^{+1} weeks
- Positive result cut off risk 1:100 (10% false positive rate)
- Preventative strategies
  - Offer aspirin 150 mg / day, ideally before 16 weeks

Costs of First Trimester Screening

- First Trimester Combined Screening test
  - Publicly funded in Australia
  - $75 / Medicare rebate ~ $27 out of pocket expense
  - May incur additional out of pocket expense for NT scan

- NIPT
  - Currently not publicly funded in Australia
  - Women pay a fee to private providers ~ $455

- Pre-eclampsia combined first trimester screening
  - Currently not publicly funded in Australia
  - PlGF done by most labs as part of CFTS (no additional cost)
  - Additional costs: Uterine artery doppler scan

Nepean Hospital: Perinatal Ultrasound Department Services

- Combined First Trimester Screening for aneuploidy
  - Available to all women
  - Includes NT Scan at no additional cost
  - Includes an early anatomy scan at no additional cost
  - Bloods may be done on site and sent to lab (DHM) OR we can provide request form
  - Blood results obtained/risk calculated within 1-3 working days
  - Directly contact patients with high-risk results for counselling appointment

Nepean Hospital Perinatal Ultrasound Department Services

- NIPT
  - Able to offer First trimester scan at no additional cost
  - If scan booked at Nepean, we are able to offer request form for labs

- Combined First Trimester Pre-eclampsia Screening
  - Available to all women who have cFTS / dating scan in hospital
  - Uterine artery doppler scan and MAP assessment at no additional cost

Summary

- Appropriate pre- and post test counselling is critical when offering screening tests
- cFTS is available to all women, and funded
- NIPT is the most accurate test for FTS but not funded
- Be aware of the limitations of NIPT
- First trimester scan is recommended regardless of choice of screening test
- Combined First Trimester PET screening has better detection for early PET and should be recommended where resources allow
- Nepean Hospital offers comprehensive first trimester screening services with no additional costs for NT scans and first trimester PET screening.

Health
Nepean Blue Mountains
Local Health District

Thank you!

Questions?