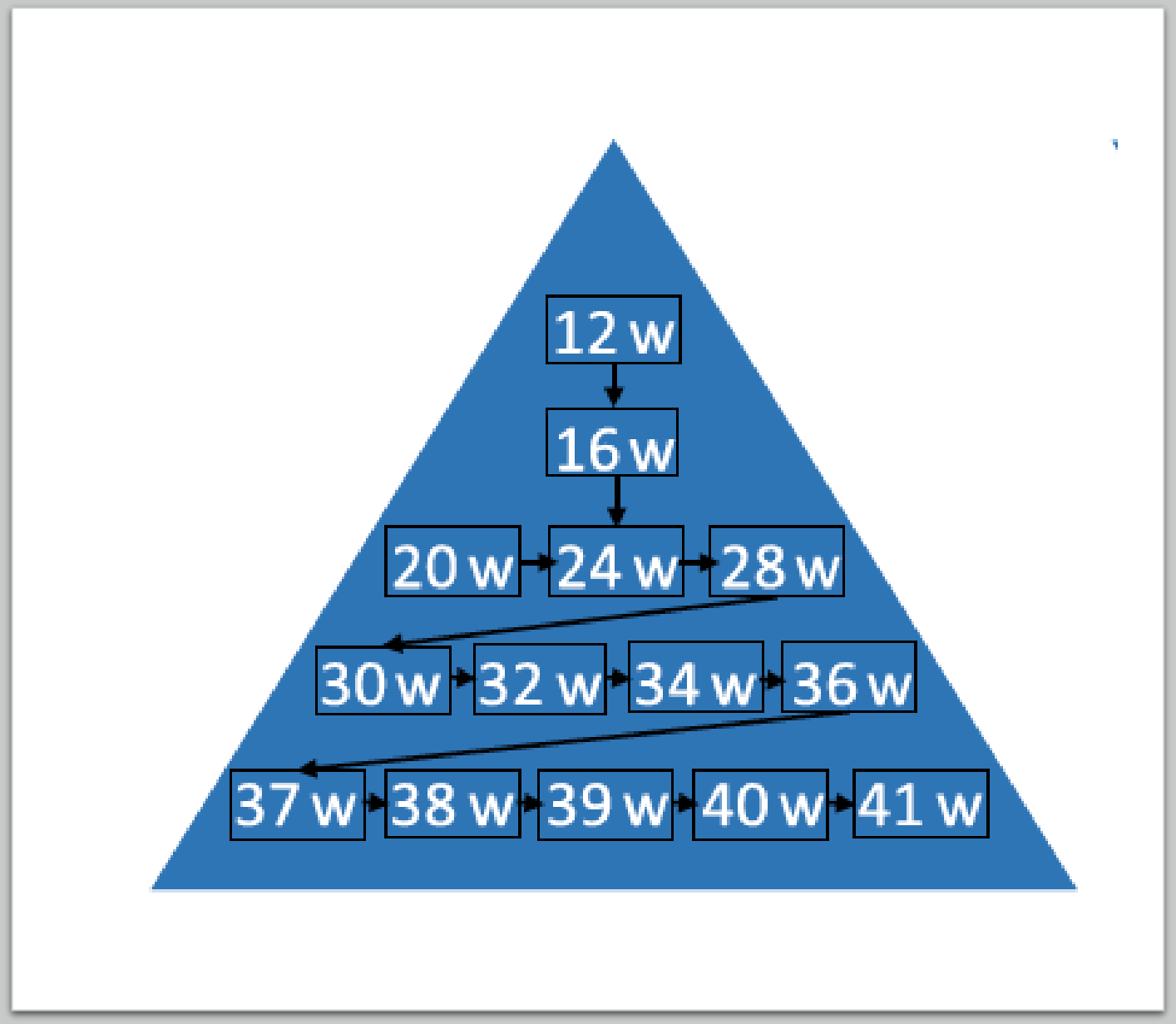
First Trimester Screening

Dr Kristine Barnden
2021



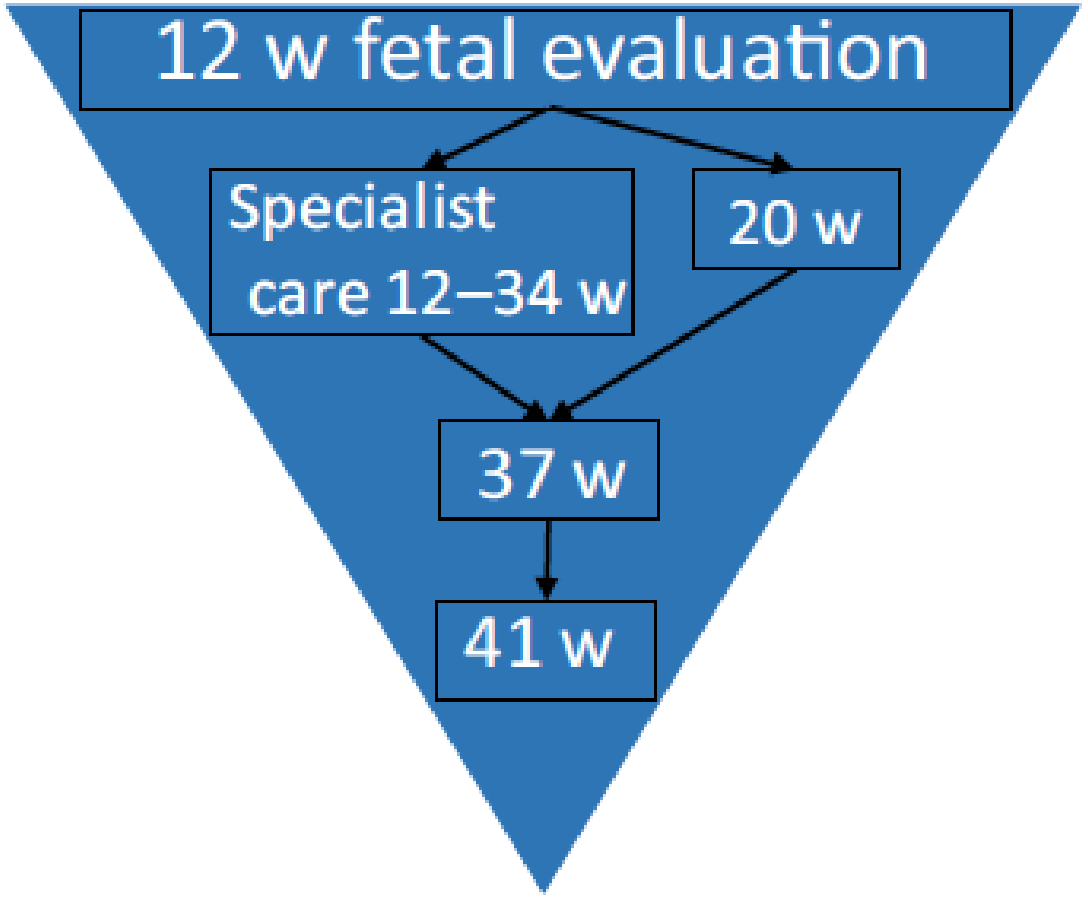
Screening for Down Syndrome

- 1970's – maternal age
- 1980's – second trimester biochemistry and 20w scan
- 1990's – combined first trimester screen
  - MA + PAPP-A + BHCG + NT

Strategy	Detection rate (%)	False positive rate (%)	# Invasive tests to detect one case T21
Maternal age (>= 35 y)	55	18 - 22	80
T2: biochemical screening	60 - 75	5 - 8	40
T1: NT alone	75 - 80	7	22
T1: NT + biochemistry	85 - 90	5	14

Value of 12-13 week scan and biochemistry

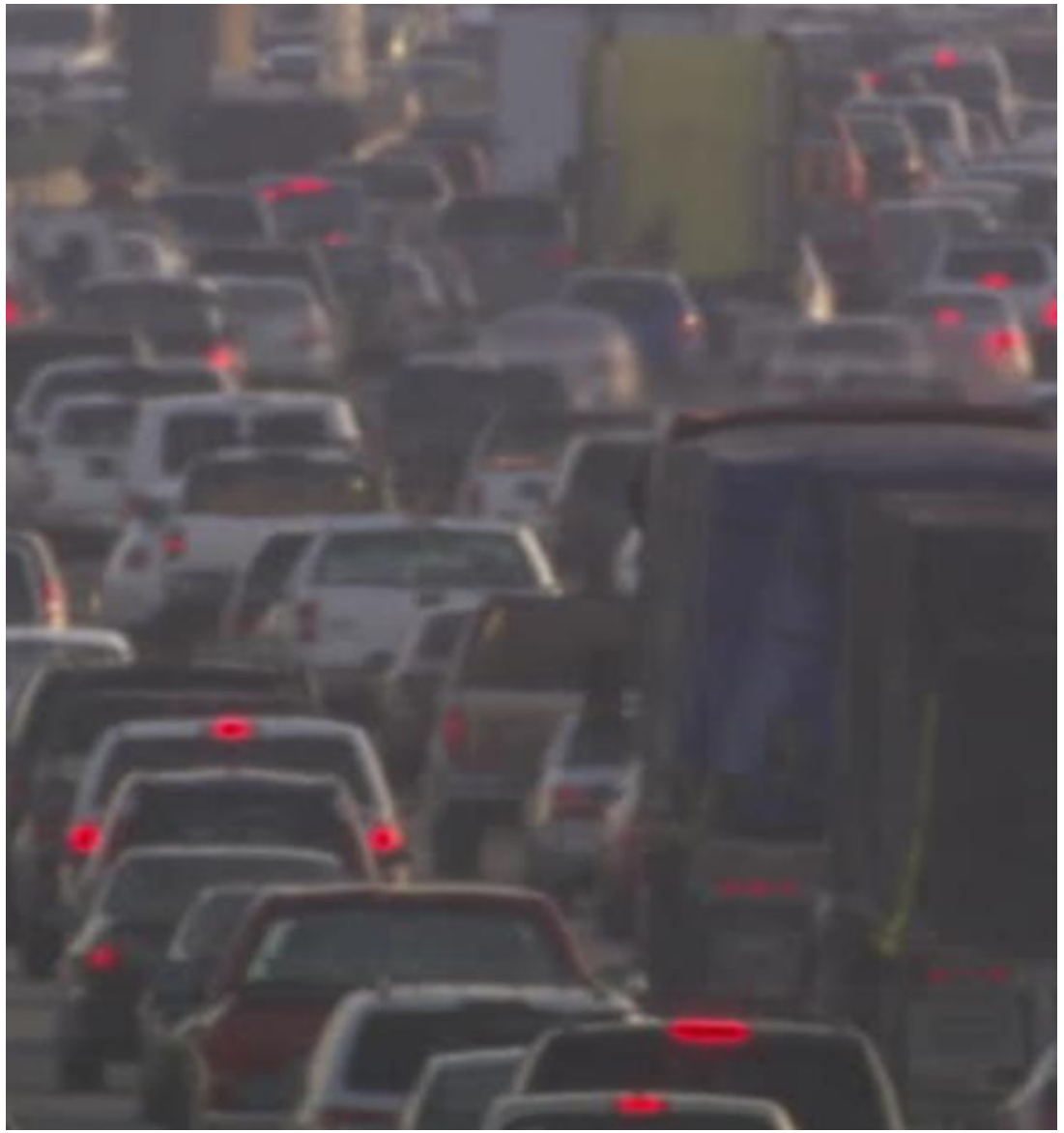
- Trisomy 21, 13, 18
- Atypical chromosomal abnormalities
- Fetal anomalies
- Screening for pre-eclampsia and FGR
- Miscarriage
- Placenta and maternal structures
- Multiple pregnancy



NIPT

- Sensitivity for Trisomy 21 >99%
- Lower rates of invasive testing
- Earlier diagnosis of aneuploidy
- Gender

cFTS vs NIPT



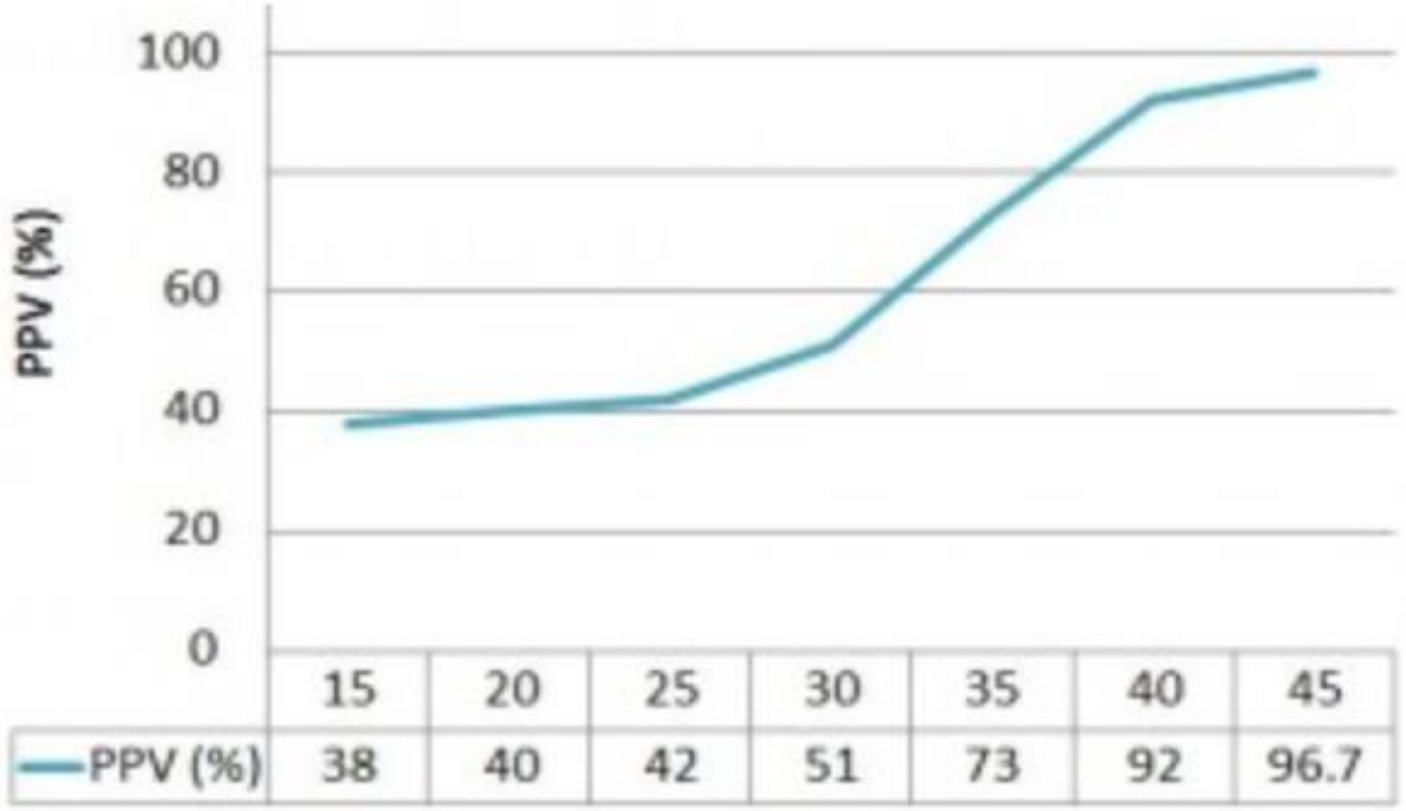
NIPT

Maternal blood test, assesses free DNA which originates from the outer cytotrophoblast of the placenta. Placental DNA and fetal DNA are identical in 98% of pregnancies.

Targeted screening for T21, T18, T13, sex chromosome aneuploidies

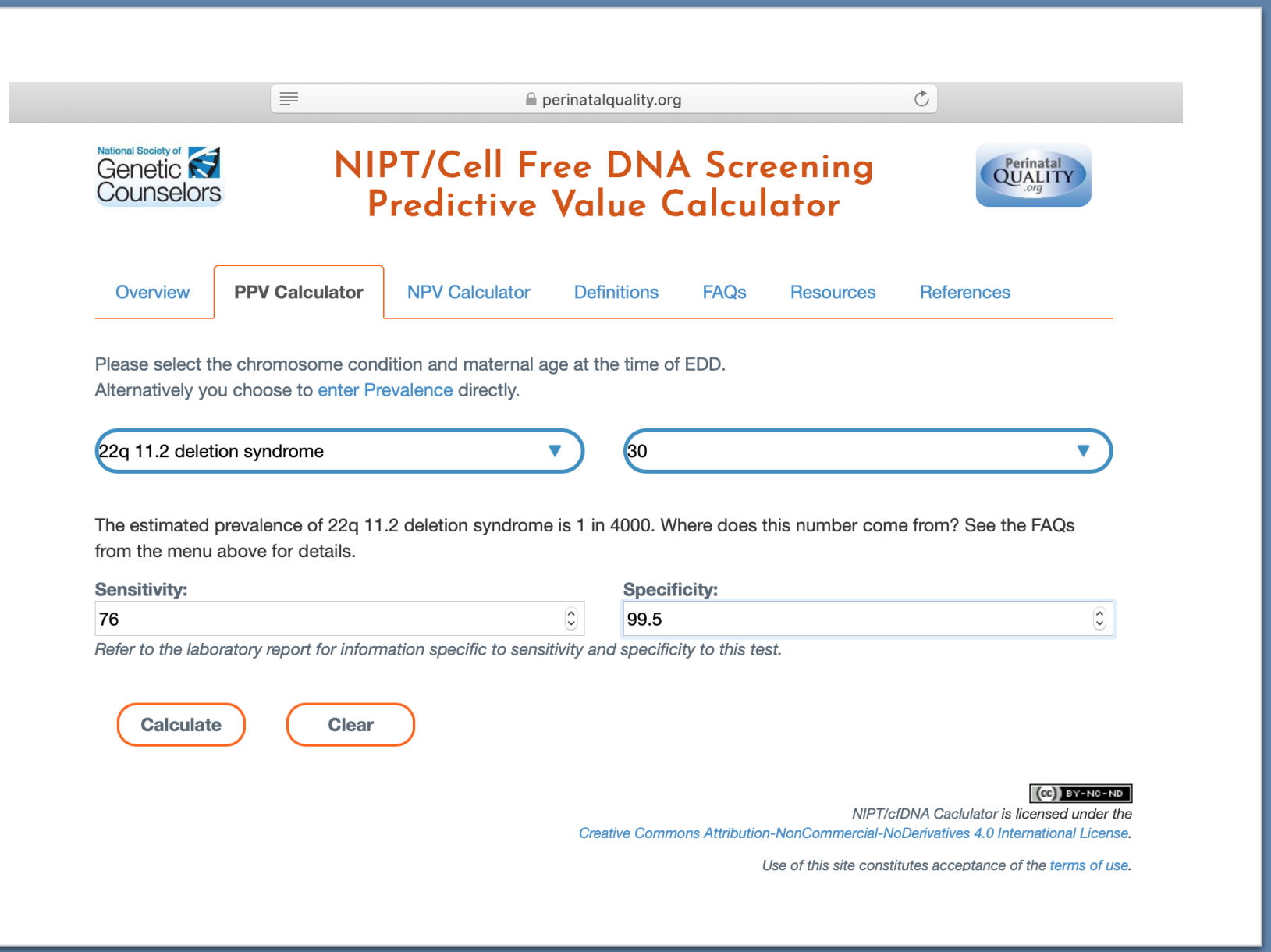
- Harmony – Sonic – also offers 22q.11.2
- Percept – VCGS – also offers “RATs” (Rare autosomal trisomies)
- Generation – TML – also offers microdeletion panel

Positive predictive value for Trisomy 21, based on age



	15	20	25	30	35	40	45
PPV (%)	38	40	42	51	73	92	96.7

Figure 2: NIPS PPV



Labs report "accuracy", but women need to know positive predictive value

perinatalquality.org

NIPT/Cell Free DNA Screening Predictive Value Calculator

Overview | **PPV Calculator** | NPV Calculator | Definitions | FAQs | Resources | References

The prevalence of 22q 11.2 deletion syndrome at 16 weeks gestation for a woman who is 30 at EDD is 1 in 4000.

The probability that result is a **true positive** (the fetus **is affected**). **PPV:** **4%**

Probability that it is a **false positive** (the fetus is **not affected**). **96%**

PPV (not rounded): 3.6617682486147887%
PPV = (sensitivity x prevalence) / ((sensitivity x prevalence) + (1 – specificity)(1 – prevalence))
PPV = (0.76 x 0.00025) / ((0.76 x 0.00025) + (1 – 0.995)(1 – 0.00025))
Please note: the post-test probability for an individual patient may differ based on other factors that influence her unique prior risk to have an affected pregnancy, such as gestational age of the patient, ultrasound findings and biochemical screening.

Calculate | Clear | Revise

NIPT Test failure – low fetal fraction

Commoner in:

- Earlier test
- High maternal BMI
- HT, ART, LMWH
- Aneuploidy risk is ~ 4x higher than background
- Increased risk adverse pregnancy outcome: miscarriage, IUFD, hypertension, prematurity

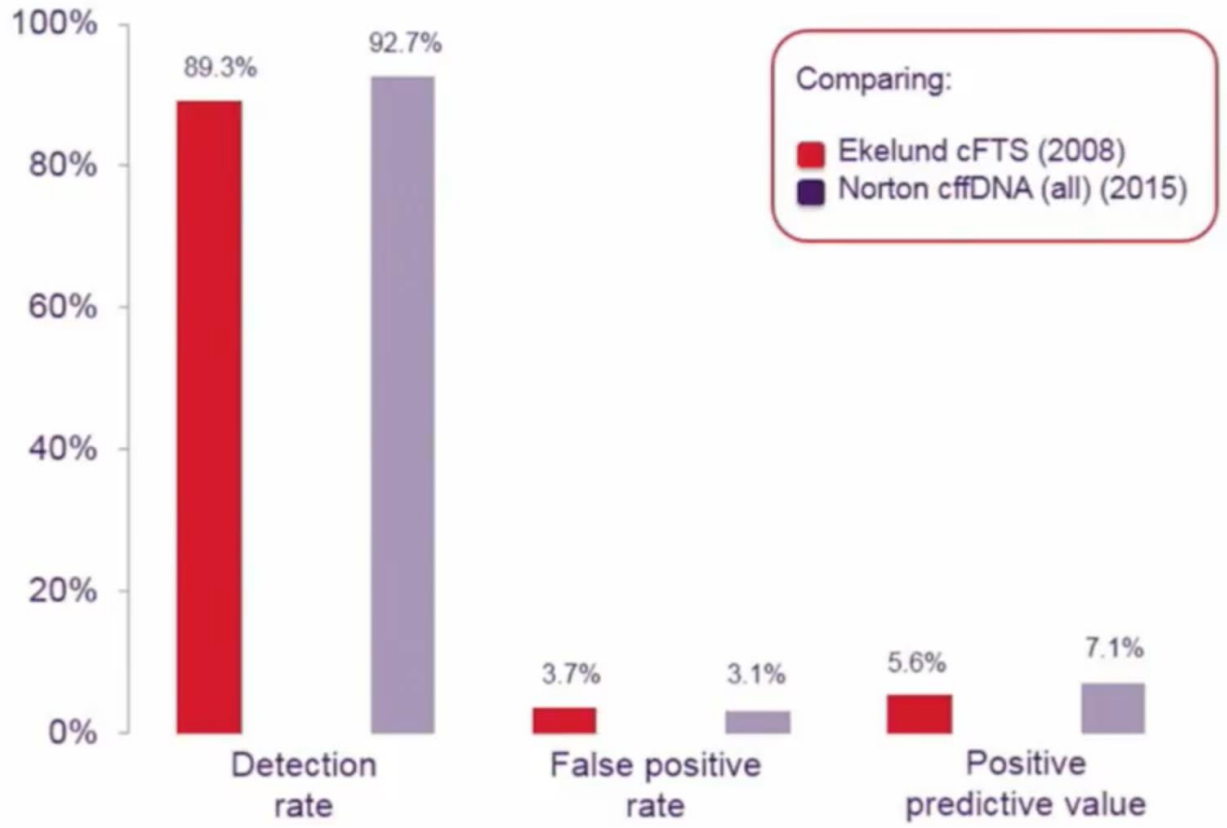
Redraw request

- women who are high risk (apriori or based on CFTS risk greater than 1:100) should be offered invasive testing
- women should have alternative screening arranged in addition to redraw if possible ie first trimester screening with biochemistry

Failed NIPT (after redraw)

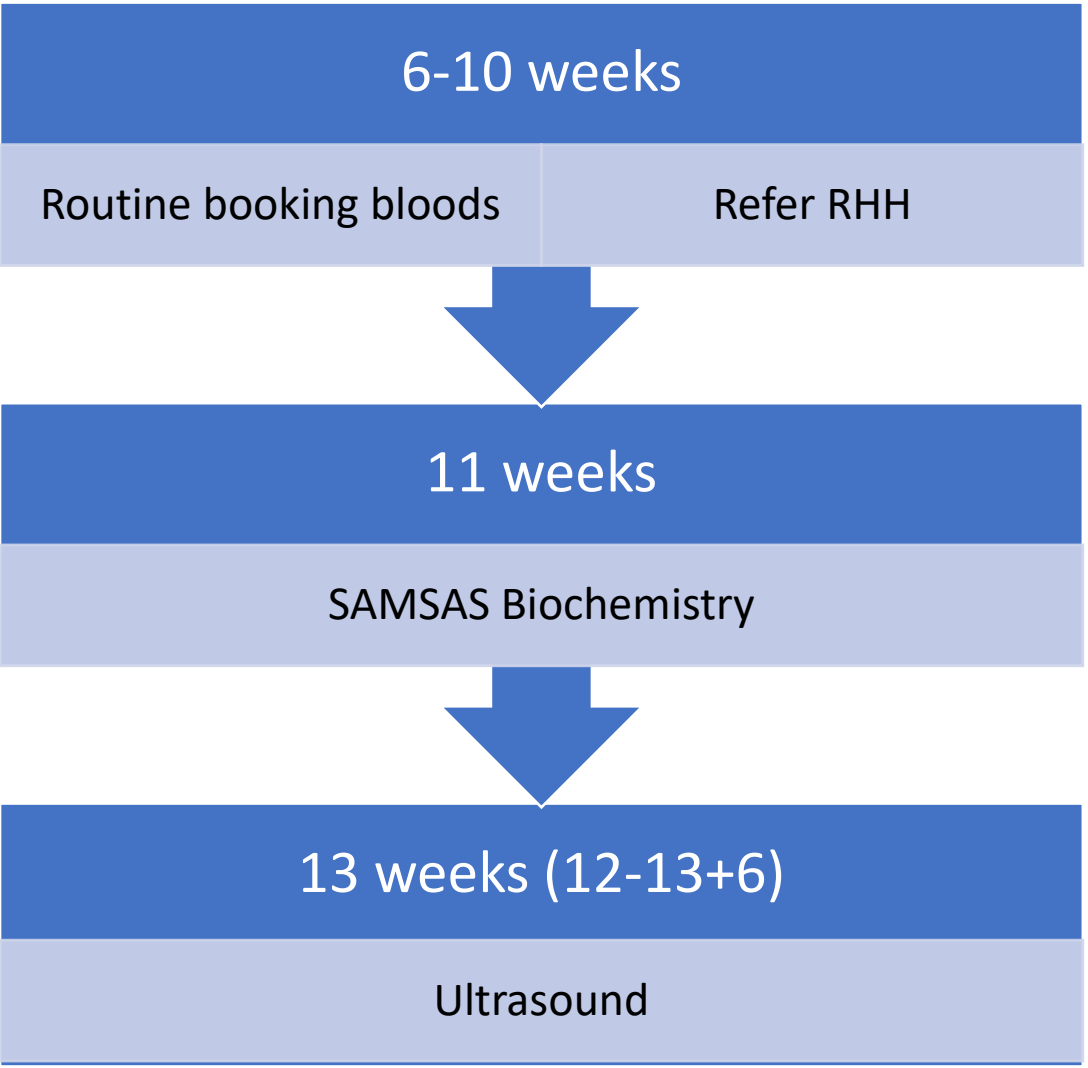
- Women should be informed of increased risk of aneuploidy and adverse pregnancy outcome
- Options should be discussed based on likely risk of aneuploidy (based on age, history, CFTS, ultrasound findings)

Screening for T21: Comparison of 'good' cFTS and 'all' cffDNA



Ekelund *et al.* BMJ 2008; Norton *et al.* 2015

- Baseline Investigations



- Optional

Genetic Carrier Screening

Dating Scan
- Uncertain dates
- Pain/bleeding/severe nausea/anxiety
- History of ectopic or recurrent miscarriage
- ≥ 2 caesareans
- NIPT as 1st line screen

NIPT as first line screen:
- Improved sensitivity for T21 (1:20,000 absolute benefit vs contingent screening)
- Earlier diagnosis
- Gender
- ? Microdeletions – low PPV, not recommended

Biochemistry through Douglas Hanley Moir

Is first trimester biochemistry necessary?

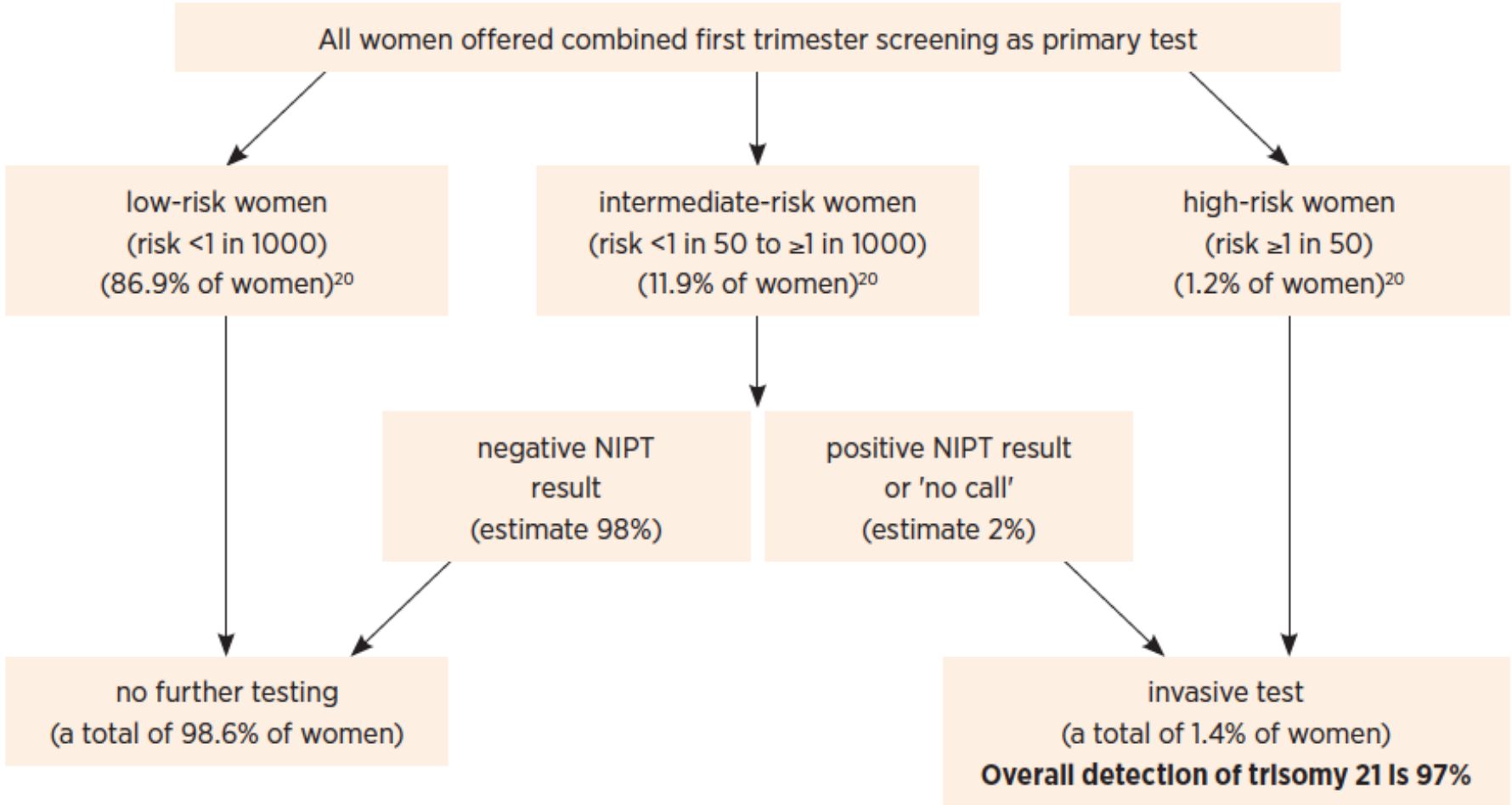
-NIPT
-declines aneuploidy screening

- All labs bulk bill – no out of pocket
- Useful for formal or informal assignment of risk for preeclampsia/FGR
- May indicate atypical genetic abnormality
- Can retrospectively do cFTS if failed NIPT

Most helpful:
- Primiparous
- Risk factors for Preeclampsia/FGR
- Increased likelihood of failed NIPT – obesity, LMWH

- Disadvantage:
  - Can cause confusion
  - Need to write clearly on request form if NIPT is planned or patient does not wish aneuploidy screening
- What about Douglas Hanley Moir?
  - BHCG, PAPP-A, AFP, PlGF: slightly increased sensitivity and specificity of preeclampsia screen and cFTS
  - Only if woman is *definitely* having scan at Women's Imaging

Fig. 2 Contingent screening model for Down syndrome



13 – 14 weeks

Fetal anomalies	Aneuploidy risk	Risk of placental insufficiency	High risk for preterm birth	High Risk for GDM
• Diagnosed or suspected on 13w scan • US markers for anomaly (NT, DV, IT) • Obstetric or family history • AFP > 2.5MoM	• High risk NIPT or cFTS • Failed NIPT or anomalous result • NT ≥ 3.4mm • BHCG < 0.2MoM or > 5MoM • PAPP-A< 0.2MoM	• History or demographic factors (NICE guidelines) • High risk pre-eclampsia screening (WI) • Uterine artery PI > 95% • PAPP-A< 0.3MoM • AFP >2.5MoM	• Previous PTB < 34 weeks • Uterine anomaly • Previous cone biopsy or ≥ LLETZ	• BMI > 30 kg/m2 • Ethnicity • Previous GDM or incr BGL • • Maternal age ≥ 40 years • Family history DM (1st degree relative or sister with GDM) • Previous (birth weight > 4500 g or > 90th percentile • Previous perinatal loss • Polycystic ovarian syndrome • Medications (corticosteroids, antipsychotics) • Multiple pregnancy
Refer MFM • Detailed scans and counselling	Refer MFM • Discuss secondary screening and invasive testing • ??Hospital funded NIPT	• Low dose aspirin (start 11-16w) • Calcium supplementation • Increased monitoring	Refer MFM • TV cervical length monitoring from 16 weeks • Progesterone for CL < 25mm, cerclage if < 15mm	POGTT 14-16 weeks

RHH Antenatal services

Routine Clinics	Pregnancy Assessment Centre (PAC)	Fetal Maternal Unit FMU	Maternal Fetal Medicine MFM
• MGP • KYM • Satellite Clinics • Doctors' Clinics (intermediate risk) • High Risk Clinic • Obstetric Endocrine Clinic • Complex Care Clinic (psychosocial)	• Ward K7E • Acute review of pregnancy complications and concerns	Wellington Centre L8 Midwifery led • Scheduled review of women requiring increased monitoring for complicated pregnancy • Fe infusions • IV fluids for hyperemesis	Wellington Centre L8 Consultant led (Lindsay Edwards, Kris Barnden, Mel Nardi, Portia Spaulding) • Tertiary ultrasound, counselling, invasive procedures

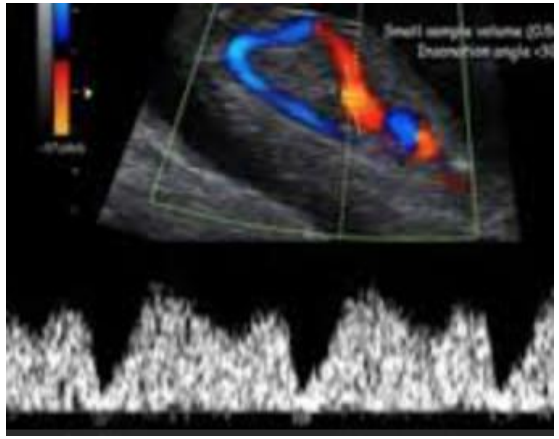
Fetal anomalies

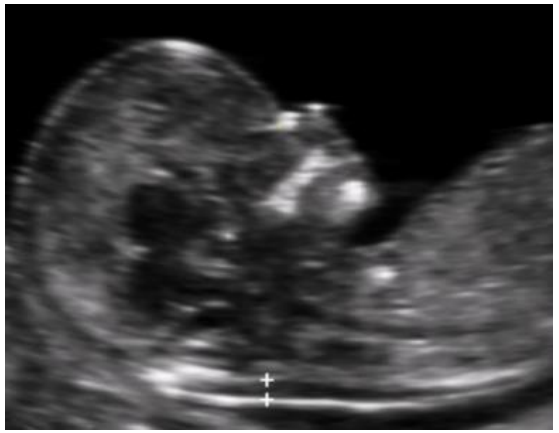
- Diagnosed or suspected on 13w scan
- US markers for anomaly
- Obstetric or family history

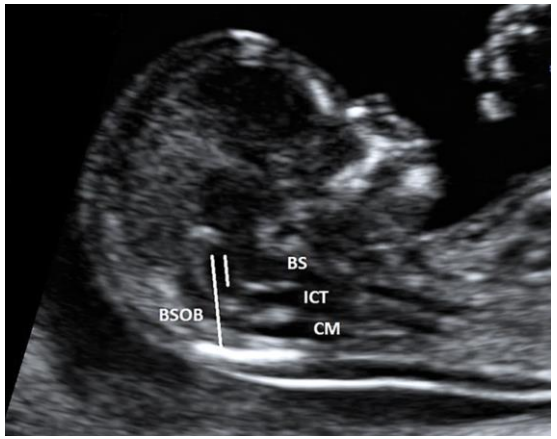
Refer MFM

- Detailed scans and counselling

- 50-60% of major anomalies are identified in the first trimester
- Variable identification rate
  - Skill and expertise of sonographer and radiologist
  - Patient characteristics (eg BMI)
  - Cardiac and brain less likely (but several markers identified)







Aneuploidy risk

- High risk NIPT or cFTS
- Failed NIPT or anomalous result
- NT ≥ 3.4mm
- BHCG < 0.2MoM or > 5MoM
- PAPP-A< 0.2MoM
- AFP > 2.5MoM

Refer MFM

- Offer invasive testing
- ??Hospital funded NIPT

- Discuss nature of condition
- Positive Predictive Value
- Diagnostic tests or further screening tests

- High risk of chromosomal anomaly, including 'atypical'
- Risk of syndromes or structural defects
- Offer detailed scans, invasive testing, ongoing monitoring

- Discuss possible causes of failure
- Risk of underlying chromosomal abnormality, including 'atypical'.
- Repeat, invasive test, secondary screen?

Hospital Funded NIPT:

- cFTS T21 likelihood 1:50 – 1:250
- NT < 3.4mm, no extremes of biochemistry
- No fetal structural abnormality
- Must be counselled in MFM or by genetic counsellor

VCGS
Leaders in Genetic Health

Victorian Clinical Genetics Services
Murdoch Childrens Research Institute
The Royal Children's Hospital
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Interpreting cFTS
with a low risk NIPT result or low PAPP-A

Introduction

When women choose to have both combined first trimester screening (cFTS) and non-invasive prenatal testing (NIPT), two separate test reports are issued. A low risk NIPT result provides very high confidence that the pregnancy is not affected by trisomy 21, trisomy 18, trisomy 13 or a sex chromosome condition. However, even when a patient has a low risk for these common abnormalities, cFTS may still provide useful information relevant to the management of the pregnancy.

Summary

NIPT is a high performance screen for the most common chromosome conditions. It is not a replacement for invasive prenatal diagnostic tests. When the cFTS risk is > 1 in 50 and/or the NT is ≥ 3.5 mm and/or there is very abnormal biochemistry, a CVS or amniocentesis should be considered. In addition, low PAPP-A may be associated with adverse obstetric outcomes.

1. Low PAPP-A (<0.45 MoM) and risk of pregnancy complications:

If a woman receives a low PAPP-A result (<0.45 MoM), a referral to a specialist O&G or specialist O&G service by 20 weeks gestation should be considered to allow for closer maternal and fetal surveillance.

A low pregnancy-associated plasma protein-A (PAPP-A) level, defined as a maternal serum PAPP-A value <0.45MoM (<5th centile), is associated with an increased frequency of adverse obstetric outcomes.1 Low PAPP-A may be indicative of poor early placentation resulting in complications such as intrauterine growth restriction (IUGR), fetal demise, preterm birth and pre-eclampsia in the third trimester.[2,3,4] The likelihood of an adverse pregnancy outcome increases as the PAPP-A level decreases as follows:

PAPP-A level	IUGR (birth weight <10th centile)	Delivery <34 weeks
<0.45 MoM (5th centile)	14% risk (odds ratio 2.7)	2.3% risk (odds ratio 2.3)
<0.29 MoM (1st centile)	24% risk (odds ratio 5.4)	2.5% risk (odds ratio 2.5)

2. Increased nuchal translucency measurement:

An invasive prenatal procedure (CVS or amniocentesis) and molecular karyotyping (microarray testing) should be offered in any pregnancy with increased NT ≥ 3.5mm +/- additional ultrasound findings.

An increased nuchal translucency (NT) measurement (≥ 3.5mm between 11+1 and 13+6 weeks gestation) is a strong marker for adverse pregnancy outcomes, even in the context of a low risk NIPT result. Fetuses with NT measurements ≥3.5mm (>99th centile) are at increased risk of a range of chromosomal abnormalities that are not detected by NIPT, especially when additional ultrasound abnormalities are present.

Even in the absence of a chromosome abnormality, increased NT can be associated with miscarriage, intrauterine death and other structural defects (e.g. cardiac, skeletal) as well as some genetic syndromes (e.g. Noonan syndrome).[5,6] Microarray testing will detect an additional 6.5-7.0% of clinically significant copy number changes in this high-risk setting when the conventional karyotype appears normal.[7]

3. Abnormal biochemistry and risk of chromosome abnormalities:

Very abnormal biochemistry levels alone may be considered as an indication for an invasive diagnostic test (CVS or amniocentesis) including the option of diagnostic prenatal microarray testing.

Abnormal levels of free β-human chorionic gonadotropin (<0.2 or ≥5.0 MoM) or very low PAPP-A levels (<0.2 MoM) have been shown to be associated with a range of chromosome abnormalities that can be detected by standard karyotype, but not by NIPT, as follows:[8]

Risk group	Risk of chromosome abnormality not detected by NIPT
PAPP-A <0.2 MoM	~4.0%
Free β-hCG <0.2 MoM	~7.0%
Free β-hCG ≥5.0 MoM	~0.5%

4. Increased cFTS risk and residual risk of atypical chromosome conditions:

When the cFTS risk is >1 in 50, an invasive procedure (CVS or amniocentesis) and molecular karyotyping (microarray testing) should be considered.

The known association between individual cFTS markers and chromosome abnormalities not detected by NIPT means women with an increased risk cFTS may also be at an increased risk of 'atypical' chromosome abnormalities (ie: not T21, T13, T18 or X/Y aneuploidy).

In a recent study, approximately 17% of women who underwent diagnostic testing following an increased risk cFTS result returned an abnormal fetal chromosome result that would not have been detected by NIPT.[9] Overall, a microscopically visible chromosome abnormality not detectable by NIPT was present in 2% of screen positive patients.

Of these abnormalities, approximately half (or 1% of all increased risk cFTS patients with low risk NIPT) would result in a viable live birth with an abnormal phenotype. These undetected atypical abnormalities may range from mild clinical outcomes to those associated with significant disability.

References

1. Management of women with a low PAPP-A, or raised nuchal translucency, with normal chromosomes. Women and Newborn Health Services, King Edward Memorial Hospital, Perth, Western Australia February 2012.

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3. Spencer K, Cowans NJ, Chefetz I, Tal J, Meiri H. First-trimester maternal serum PP-13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of pre-eclampsia. Ultrasound Obstet Gynecol. 2007; 29 (2): 128-34.

4. Smith GCS, Stenhouse EJ, Crossley JA, Aitken DA, Cameron AD, Connor JM. Early pregnancy levels of pregnancy-associated plasma protein A and the risk of intrauterine growth restriction, premature birth, preeclampsia and stillbirth. J Clin Endocrinol Metab 2002; 87:1762–7.

5. Souka AP, Krampl E, Bakalis S, Heath V, Nicolaides KH. Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. Ultrasound Obstet Gynecol. 2001 Jul; 18(1): 9-17.

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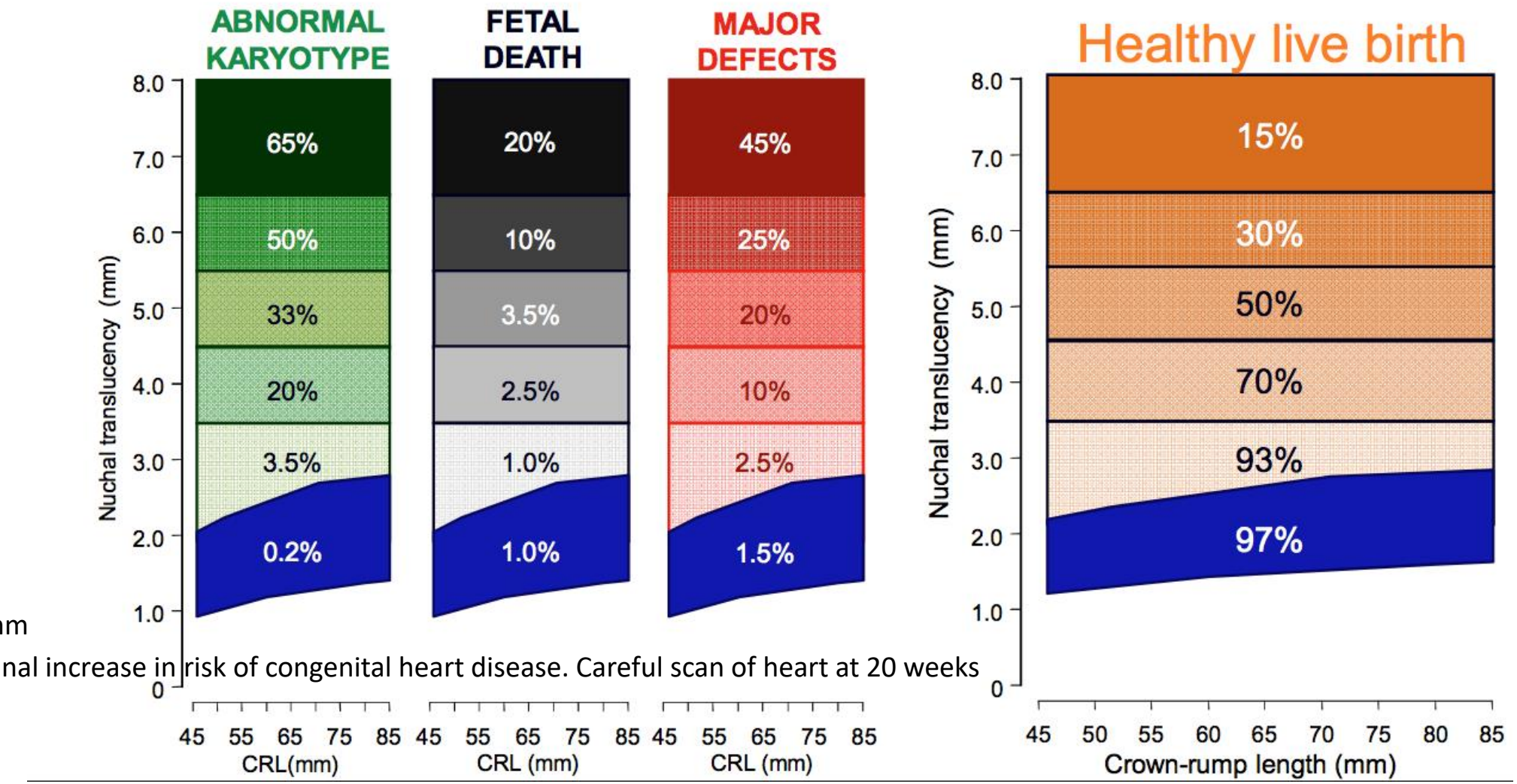


- NT 3 – 3.4mm
  - Marginal increase in risk of congenital heart disease. Careful scan of heart at 20 weeks

Risk of placental insufficiency

- History or demographic factors (NICE guidelines)
- High risk pre-eclampsia screening (WI)
- Uterine artery PI > 95%
- PAPP-A< 0.3MoM

- Low dose aspirin (start 11-16w)
- Calcium supplementation
- Increased monitoring

NICE GUIDELINES

Women are at an increased risk of pre-eclampsia if they have 1 high risk factor or more than 1 moderate risk factor for pre-eclampsia.

High risk factors include:

- hypertensive disease in a previous pregnancy
- chronic kidney disease
- autoimmune disease, such as systemic lupus erythematosus or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

Moderate risk factors include:

- first pregnancy
- age 40 years or older
- pregnancy interval of more than 10 years
- body mass index (BMI) of 35 kg/m^2 or more at first visit
- family history of pre-eclampsia
- multi-fetal pregnancy.

Risk of placental insufficiency

- History or demographic factors (NICE guidelines)
- High risk pre-eclampsia screening (WI)
- Uterine artery PI > 95%
- PAPP-A< 0.3MoM

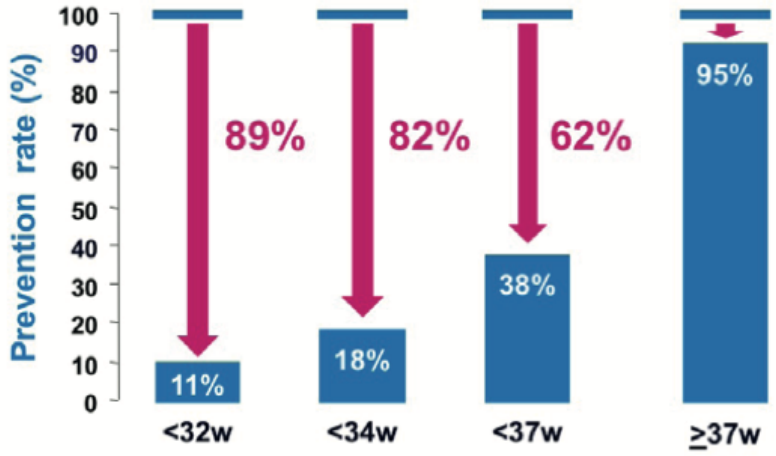
- Low dose aspirin (start 11-16w)
- Calcium supplementation
- Increased monitoring

- In a multicentre, randomized, placebo-controlled trial involving women at high risk for preterm preeclampsia, treatment with low-dose aspirin initiated at 11 to 14 weeks of gestation was associated with a lower incidence of this diagnosis.
- Risk determined by FMF software: BP, PAPP-A, PlGF, UtA PI
- Cut-off 1:100
- Randomised to placebo or aspirin 150mg nocte from 11-14 to 36 weeks gestation
- Rolnik D et al, NEJM, Aug 2017

The Fetal Medicine Foundation

ASPRE project

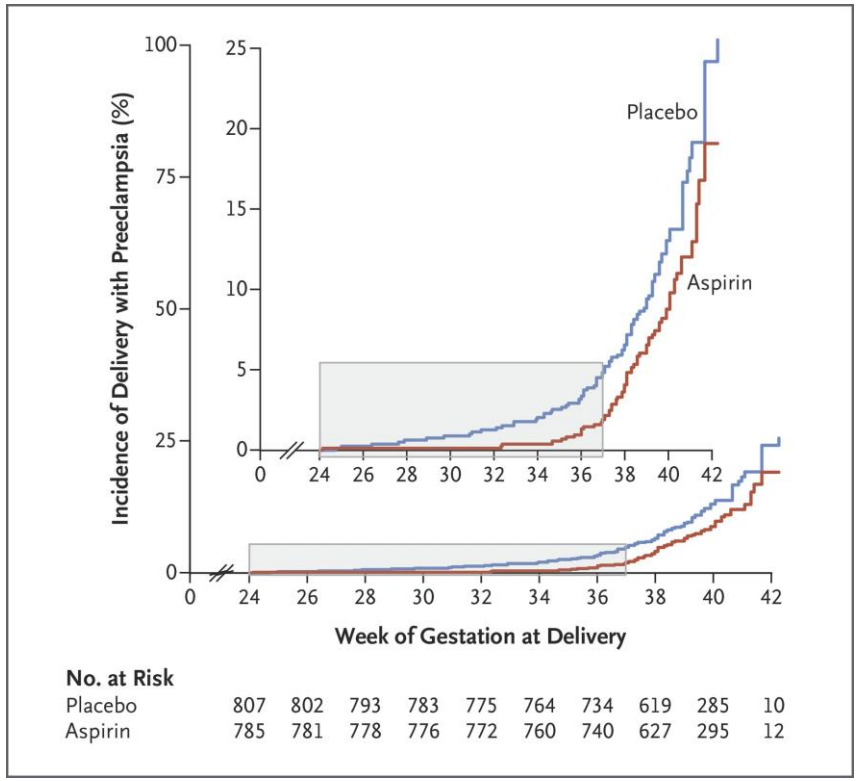
Prevention of preeclampsia



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.

Low dose aspirin



Low dose aspirin in pregnancy

Low dose aspirin may be recommended to pregnant women to reduce the risk of certain conditions that are related to abnormal development of the placenta.

Low dose aspirin is usually commenced between 12 and 16 weeks of pregnancy (but may occasionally be started later), and continued to 36 weeks.

The recommended dose is 100 - 150mg every day, taken at night.

Aspirin is available in 100mg or 300mg tablets. If your doctor has recommended a daily dose of 150mg, take half of a 300mg tablet, and throw the remaining half away, as the tablets become less effective if not taken immediately.

Taking low dose aspirin has been shown to reduce the risk of:

- developing hypertension (high blood pressure) and pre-eclampsia (high blood pressure associated with a range of potentially dangerous pregnancy complications)
- giving birth to your baby prematurely (before 37 weeks)
- your baby being smaller than expected
- infant death around the time of birth
- having a pregnancy with a serious adverse outcome

Studies have not shown any harm from taking low dose aspirin in pregnancy, but larger doses should be avoided. Aspirin should not be used to treat fever or pain in pregnancy.
Aspirin can affect (and be affected by) other medications, including over the counter medications and herbal remedies. Please discuss any other medications you are taking with your midwife, GP, obstetrician or pharmacist.

There is no evidence that taking low dose aspirin increases the severity of COVID-19 infection.

Side effects
Taking low dose aspirin can cause mild indigestion. If you take your aspirin either with or just after food, it will be less likely to upset your stomach. Avoid taking aspirin on an empty stomach.

There is no evidence to suggest low dose aspirin causes any significant increase in bleeding during pregnancy. There may be a slightly increased risk of excess bleeding after delivery for women taking aspirin. If you have any questions or concerns about taking low dose aspirin please speak to your obstetrician, GP or midwife.

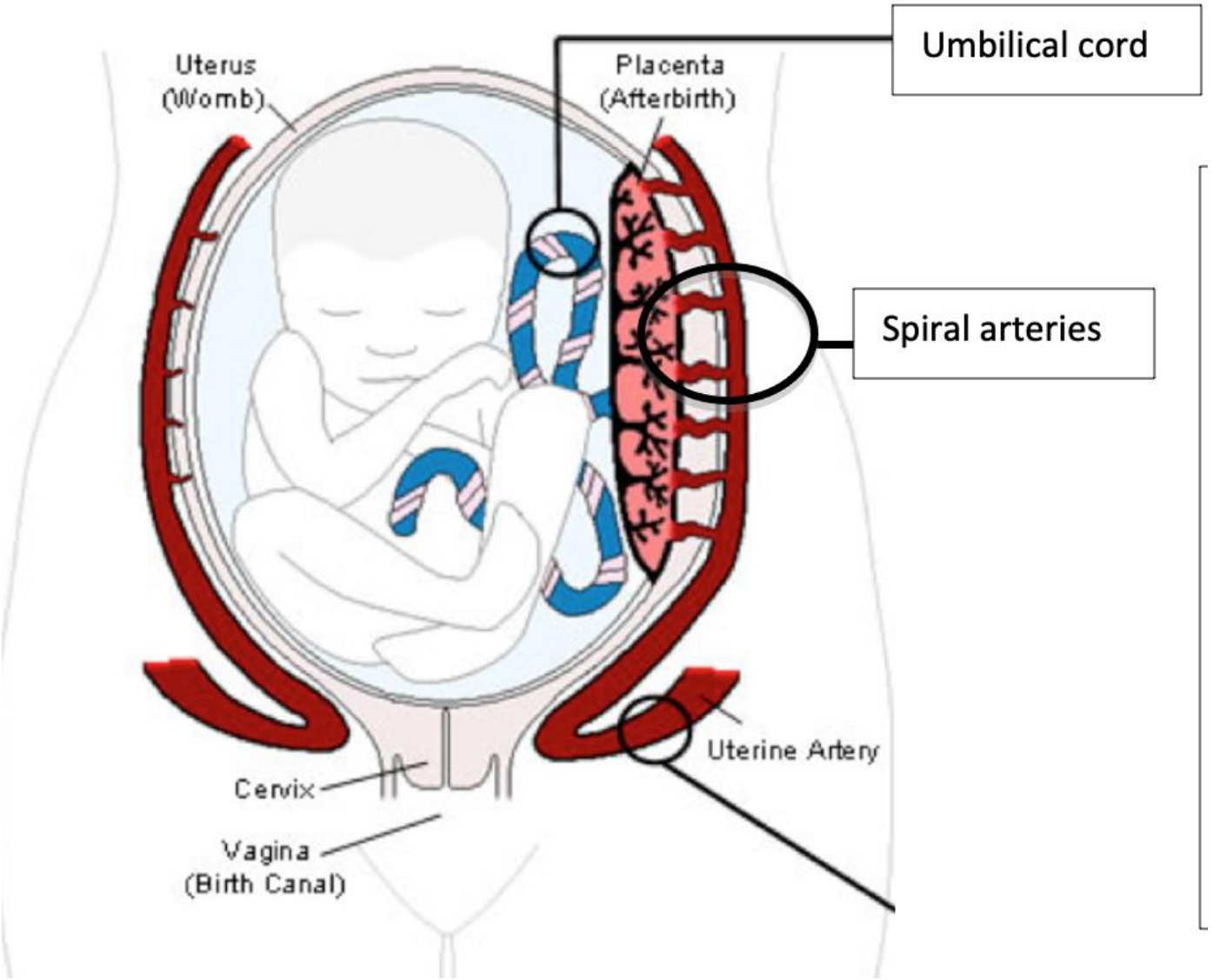
Allergies
Please tell your obstetrician and GP if you are allergic to aspirin (or other anti-inflammatory medications (NSAIDS)), or if you have severe asthma, chronic kidney problems, stomach ulcers, or have been previously advised not to take aspirin or other NSAIDs.

As with any medicine, you should seek urgent medical assistance if you experience serious side effects such as wheezing, swelling of the lips, face or tongue or sudden or severe itching, skin rash or hives.

Further information
If you would like more information about taking low dose aspirin in pregnancy, your midwife or obstetrician will be happy to answer your questions and advise you.

Placental insufficiency (Preeclampsia/FGR): prevention and monitoring

- Low dose aspirin, 100-150mg nocte, <16w to 36w
- Calcium supplementation
  - Dietary: >900mg/day or ≥ 5 serves high calcium food
  - 2 -3 tablets (600mg) calcium daily
- Lower stress, regular gentle exercise
- Healthy diet
- Serial growth scans in 3rd trimester
- Report symptoms and signs of preeclampsia, reduced fetal movements

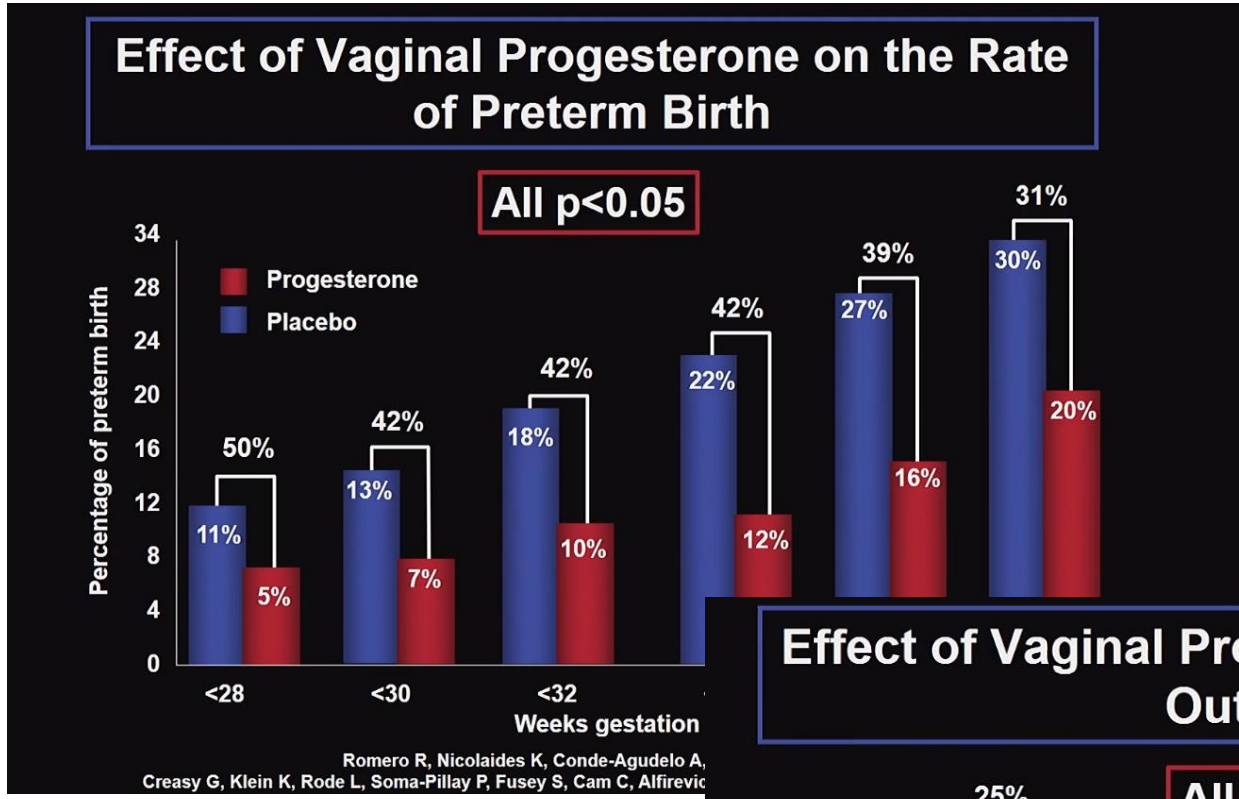


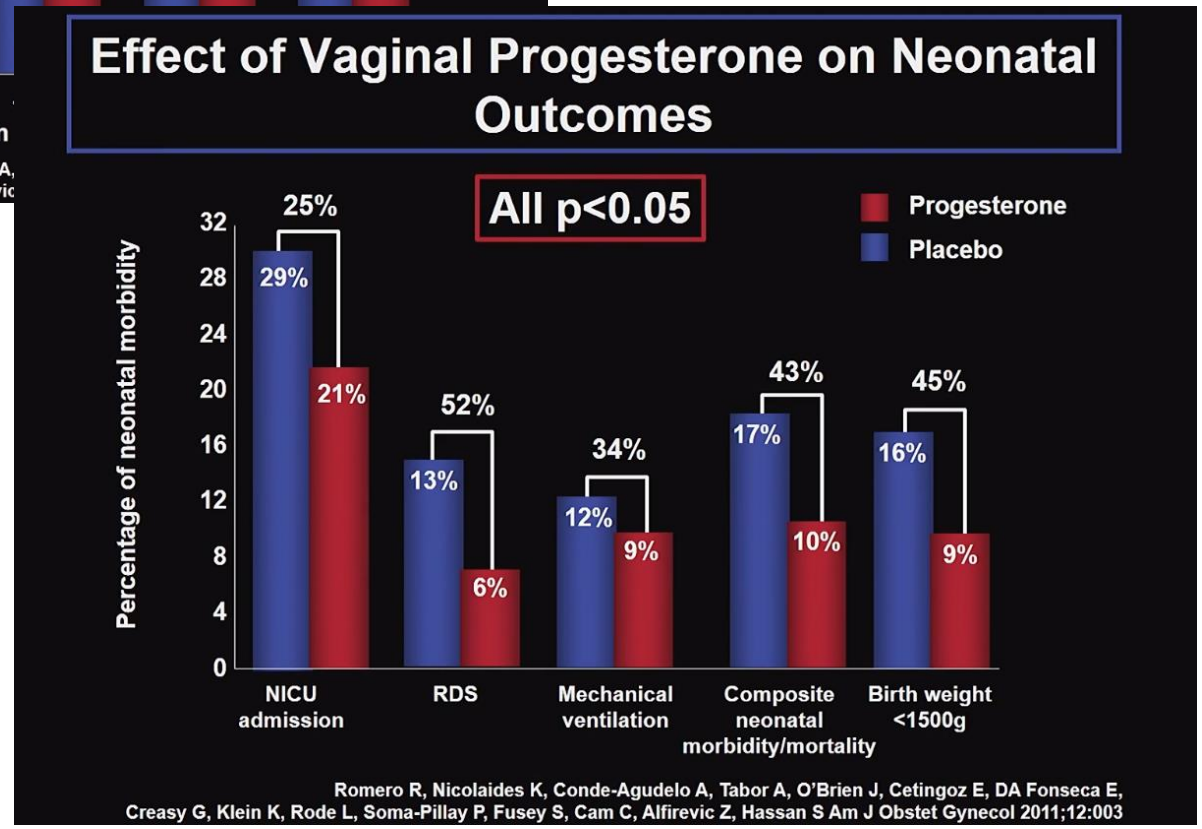
High risk for preterm birth

- Previous PTB < 34 weeks
- Uterine anomaly
- Previous cone biopsy, ≥2 LLETZ

Refer MFM

- TV cervical length monitoring from 16 weeks
- Progesterone for CL < 25mm, cerclage if < 15mm





New Developments

And this is the latest breakthrough: 5D ultrasound... with 95% accuracy
this is a realistic representantion of your cute little baby 20 years from now