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CHAPTER 1 Prenatal screening for aneuploidy and neural tube defects

- Multiple marker screening uses a combination of maternal age and 2 or more biochemical tests, with or without an USS, to produce a single result for risk of Down syndrome, trisomy 18, and open neural tube defects (ONTDs).
- A screen is positive when the risk of one or more of the screened disorders falls above a designated risk cut-off.
- **A risk cut-off** – The risk of the condition being present in the fetus at term or at mid-trimester. The risk for the latter will be higher, because 23% of fetuses with Down syndrome are lost between mid-trimester and term (risk cut-off of 1:350 at term would be similar to 1:280 at mid-trimester).

- Detection rate (DR) or sensitivity: The proportion of affected individuals with positive screening results.
- False-positive rate (FPR): The proportion of unaffected individuals with positive screening results. It is the complement of the specificity.
- As screening performance improves, the FPR decreases and/or the DR increases.
- Multiples of the median (MoM): The absolute value of the assayed marker (serum or NT) divided by the gestation-specific median value of the serum marker in the measuring laboratory or by using standard or sonographer-specific curves for NT. This allows direct comparison of results between programmes.

Maternal age

- In the past screening was offered only to women ≥ 35 years at the EDD. This was considered to be the point at which the risk of a pregnancy loss was less than the chance of identifying a pregnancy with a significant chromosomal abnormality.
- The probability of conceiving a fetus with a trisomy increases with maternal age. However, maternal age screening is inferior to the use of multiple biochemical markers \pm a first trimester USS NT assessment. The latter provides a greatly reduced FPR with a substantially improved DR across all age groups.
- **Do not use maternal age alone for prenatal screening for aneuploidy.**
- Do not offer amniocentesis to women ≥ 40 years without prior screening, because with a negative screening result, their risk of a chromosomal abnormality remains $< 1/200$.

Factors potentially affecting screening performance

Gestational dating – USS improves the precision of gestational age estimation, and reduces the error for each screening marker. This effect is greater for markers whose concentrations change most with gestational age. For all marker combinations, the FPR is lower by about 2% when gestational age is estimated using a scan.

Insulin-dependent diabetes mellitus – Some second trimester serum markers tend to be lower in women with IDDM. After weight correction, AFP is $\sim 10\%$ lower and uE3 is $\sim 5\%$ lower in diabetic women. NT measurement, free β -hCG, and PAPP-A are not affected.

Ethnic origin – Adjusting for ethnic origin slightly increases the DR for a given FPR. Statistically significant differences in NT measurement have been found between ethnic groups. However, these differences may be too small to warrant correction.

Maternal weight – There is a negative association between the levels of maternal serum markers and maternal weight. With second trimester screening, maternal weight adjustment increases DR by about 1% for a given FPR.

- Weight adjustment is beneficial if there is a marginally elevated AFP when screening for ONTD. Weight adjustment does not appear to be necessary for NT risk adjustment, because it increases by only a clinically insignificant amount with increasing maternal weight.

Assisted reproduction – In the first trimester, a lower value of PAPP-A has been reported in IVF pregnancies, but data on NT and first trimester free β -hCG remain inconsistent.

Invasive prenatal diagnosis

- Offer to women who are at increased risk of fetal aneuploidy:
 - * Non-invasive screen result above the risk cut-off.
 - * Ultrasound findings.
 - * A history of a previous child or fetus with a chromosomal abnormality.
 - * Woman/her partner is a carrier of a chromosome rearrangement that increases the risk of having a fetus with a chromosomal abnormality.
- In these scenarios, the risk of a chromosomal abnormality not detected by screening is high enough to offer invasive testing without prior screening.

Screening options

Screen should provide – A DR for Down syndrome of 75% with <3% FPR in the first trimester (UK and SOGC) and a DR of 75% with <5% FPR in the second trimester (SOGC).

First trimester screening

Nuchal translucency (NT)

- NT – The subcutaneous layer of fluid behind the fetal neck and lower cranium visualized on ultrasound. It has a DR for Down syndrome ranging from 69 to 75%, with an FPR of 5–8%.
- Raised NT is also associated with numeric chromosome abnormalities, fetal anomalies such as cardiac defects, diaphragmatic hernia, and single gene disorders associated with decreased fetal movement.
- An NT > 99th percentile has a sensitivity of 31% and specificity of 99% for major congenital heart defects when the fetal karyotype is normal. 1 in 33 fetuses with an NT > 95th percentile and 1 in 16 with an NT > 99th percentile have a major cardiac defect.
- Increased NT at 11–14 weeks with a normal fetal karyotype is an indication for a detailed USS at 18 to 20 weeks, to assess the fetal heart, including a 4-chamber view and view of the outflow tracts or a fetal echocardiogram.

First trimester combined (FTC)

- **Maternal age + NT + hCG + PAPP-A**
- 2 first trimester maternal serum biochemical markers: PAPP-A and hCG (total). PAPP-A is lower in Down syndrome pregnancies and hCG is higher.
- Combination of the maternal age-related risk, maternal serum PAPP-A, and free β -hCG provides a DR of 61% for Down syndrome, with a 5% FPR.
- Combination of the 2 first trimester biochemical markers with NT has a significant improvement over second trimester triple and quadruple screening.
- FTC detects 78% of cases with a 3% FPR using a term risk cut-off for Down syndrome of 1:300 (83% DR with a 5% FPR).
- FTC also screens for trisomies 13 and 18.

Nasal bone

- USS screening for delayed ossification of the fetal nasal bone in the first or second trimester.
- The first trimester USS, which determines the presence or absence of the nasal bone between 11 and 14 weeks of gestation, may be likely to be incorporated into other screening modalities. It detects 77% of Down syndrome cases.
- The difficulty in performing first trimester nasal bone sonography consistently in the general population might limit the usefulness of this screening technique.

Recommendations

- Given that timing is critical for serum analysis, accurate dating of the pregnancy is very important. Perform USS dating if menstrual or conception dating is unreliable. For any abnormal serum screen calculated on the basis of menstrual dating, perform an USS to confirm gestational age.
- Do not incorporate evaluation of the fetal nasal bone in the first trimester as a screening unless it is performed by sonographers trained and accredited for this service.
- For women who undertake first trimester screening, offer second trimester serum AFP screening and/or USS to screen for ONTDs.
- If local USS services are unable to provide a comprehensive screen for NTDs at 18 to 20 weeks' gestation, in patients undergoing first trimester screening for aneuploidy, offer MSAFP in the second trimester to screen for NTDs.

Second trimester screening

Triple marker testing

- Maternal age + MSAFP + unconjugated oestriol (uE3) + hCG measured between 15 and 20 weeks' gestation would detect 65% of fetuses with Down syndrome with a 5% FPR.
- Using a term risk cut-off of 1:385, the triple marker screening detects 72% of fetuses with Down syndrome with a 7% FPR.
- It also screens for ONTDs, other open fetal defects (e.g., gastroschisis, omphalocele), placental dysfunction, Smith–Lemli–Opitz syndrome, and trisomy.

Quadruple testing

- Maternal age + MSAFP + uE3 + hCG + Inhibin A
- Inhibin A will increase the DR of Down syndrome by 10%.
- With a risk cut-off of 1:230 at term, the DR is 75–80%, and the FPR is lowered to 3–5%.

Combined first and second trimester

Integrated prenatal screening (IPS)

- PAPP-A and NT in the first trimester and the quad screen in the second trimester, with results released when all the testing completed.
- DR of 85–87% with an FPR of 0.8–1.5%.
- When Inhibin A is excluded from the IPS, the FPR increases to ~2.5%.
- The benefit of IPS over FTS is the achievement of a lower FPR and reduction of the number of invasive diagnostic procedures needed. However it requires two visits and delays results.
- IPS also screens for ONTDs and trisomy 18.

Serum integrated prenatal screening

- PAPP-A in the first trimester and triple or quad screening in the second trimester.
- This has an 83% DR for Down syndrome for a 4% FPR.
- Alternatively, PAPP-A and free β -hCG can be offered in the first trimester, followed by AFP and uE3 in the second with the same performance. The FPR is 4.2% if PAPP-A is measured at 10 completed weeks, and the FPR is doubled (8.5%) if it is measured at 13 completed weeks.
- Serum IPS is a practical option for areas where there is limited or no access to NT screening.

Other screening options

Contingent screening

- Majority of women receive their result after FTC. Women at high risk (risk $> 1/50$) are offered invasive testing, and women at low risk (risk $< 1/1500$) require no further testing. A proportion of women with a risk between the two cut-offs (1/50 and 1/1500) will go on to have second trimester screening and will receive a combined result.
- It is possible to select risk cut-offs that achieve performances similar to IPS, thus meeting the guideline recommendation, while achieving detection of a significant proportion of abnormal pregnancies by the end of the first trimester.
- It is suggested that contingent screening strategy had the best cost-effectiveness ratio, with fewer procedure-related euploid miscarriages and unnecessary terminations.
- However, the women in the intermediate risk group are likely to experience raised anxiety, and a proportion of them might wish to have an invasive test immediately.

Non-invasive prenatal testing (NIPT)

- Cell-free fetal DNA (cffDNA) comes from the placenta and can be detected from the first trimester of pregnancy onwards in maternal circulation. This technology is likely to become the primary screen for chromosomal abnormalities in pregnancy. This will enhance the information available to pregnant women while greatly reducing the loss of uncomplicated pregnancies as a result of miscarriage caused by unnecessary invasive procedures. NIPT is not considered diagnostic as yet. Results from an ongoing study will be used to assess the accuracy of NIPT in the lower-risk population, as the majority of previous studies have looked at high-risk women only. Further evaluation is being undertaken by the UK NSC before it considers whether to adopt NIPT in the NHS.

UK National Screening Committee (UKNSC) recommendations for Down syndrome screening programme

- Offer all women screening test(s) with an FPR of <3% and a DR of >75%.
- Screen in the time window of 10 weeks + 0 days to 20 weeks + 0 days' gestation.
- Preferred strategy is to complete screening by 13 weeks + 6 days' gestation.
- Presently there is insufficient evidence for screening strategies for Down syndrome prior to 10 weeks of pregnancy.

First trimester combined (FTC)

- NT + hCG, PAPP-A (same time).
- Early diagnosis; screening is completed in one stage; gives a risk before 14 weeks of pregnancy allowing earlier decision making.
- Biochemistry or USS alone before 13 weeks will not meet the 2007 recommendation for DR.

Integrated testing (IT)

- NT + PAPP-A (1st trim.); hCG (all types), uE, and AFP (2nd trim.).
- Woman needs to attend twice for screening and has to wait until both samples have been processed for a final result.

Serum integrated testing (SIT)

- PAPP-A (1st trim.); hCG (all types), uE, and AFP (2nd trim.).
- Requires two visits but does not include USS NT.
- Women need to wait for a final result.

Quadruple testing (QT)

- hCG (all types), uE3, AFP, and Inhibin A.
- Tests in the second trimester for those women who book late (around 15% of the pregnant population).
- The second trimester screening test that just meets the 2007 recommendation for DR and FPR is the quadruple test.

The full screening window for:

- First trimester PAPP-A test – 10 weeks + 0 days to 13 weeks + 6 days.
- NT measurement – 11 weeks + 0 days to 13 weeks + 6 days.
- Second trimester serum testing – 15 weeks + 0 days to 20 weeks + 0 days.
- The optimal time for the PAPP-A measurement is 9–10 weeks' gestation with the performance of PAPP-A decreasing between 10 and 13 weeks. The proportion of pregnancies in which a satisfactory NT measurement can be obtained is the highest at 11 to 13 weeks' gestation. First trimester measurements are usually carried out between 11 and 14 weeks' gestation as a compromise to make the timing favourable for NT and PAPP-A.

- Offer the 'First trimester combined test' between 11 weeks 0 days and 13 weeks 6 days. For women who book later in pregnancy, offer the most clinically and cost-effective serum screening test (triple or quadruple test) between 15 weeks 0 days and 20 weeks 0 days. (NICE, CGN 62; 2008).
- **Threshold levels for risk measurements** – Categorize individual results as higher or lower risk based on a cut-off of 1 in 200 at term for second trimester screening strategies and 1 in 150 at term for first trimester screening strategies.
- Offer a confirmatory diagnostic test for all screen positive results – amniocentesis/CVS.
- **Benchmark timeframe:**
A DR for Down's syndrome of >75% with a FPR of <3% (April 2007 to April 2010).
A DR of >90% with a FPR of <2% (by April 2010).

This chapter is based on:

Prenatal Screening for Fetal Aneuploidy in Singleton Pregnancies; 2011; Joint SOGC–CCMG Clinical Practice Guidelines.
 Screening for Down's syndrome: UK NSC Policy recommendations 2011–2014; Model of Best Practice; NHS Fetal Anomaly Screening Programme.
 Antenatal Care – NICE Clinical Guideline 62; 2008.
 Non-invasive prenatal testing for chromosomal abnormality using maternal plasma DNA. RCOG Scientific Impact – Paper No. 15; March 2014.
www.rapid.hhs.uk

CHAPTER 2 Routine fetal ultrasound screening

Use of first trimester USS

As part of prenatal screening, 11- to 14-week ultrasounds should be offered on a routine basis. (NICE CGN 62; 2008)

Indications/benefits

Accurate dating

- Crown–rump length (CRL) at 8–12 weeks is the most accurate method to date pregnancy; predicts the expected date of birth to within 5 days.
- It decreases the number of labour inductions for post-term pregnancy and helps to determine the timing of planned CSs to prevent iatrogenic prematurity.
- It is important to assess fetal growth and interpret maternal serum screening.
- First trimester USS is indicated when LMP date is uncertain.

First trimester TOP

- It is associated with lower maternal morbidity than second trimester termination procedures. An inaccurate estimation of gestational age can be avoided by ultrasound examination prior to procedure selection.

Diagnostic or therapeutic procedures

- First trimester USS is recommended for suspected ectopic pregnancy, molar pregnancy, and suspected pelvic mass.
- First trimester USS is recommended during diagnostic or therapeutic procedures requiring visual guidance (e.g., CVS, amniocentesis) and prior to cervical cerclage placement.

Multiple gestation

- USS examination should include number of fetuses, viability, CRLs, chorionicity or amnionicity, and NT assessment.
- Maternal serum screening for aneuploidy is not effective and an NT assessment of risk for each fetus is recommended.
- The accurate diagnosis of a chorionicity in twin pregnancy is important because it selects a subgroup of twin pregnancies at higher risk for twin-to-twin transfusion syndrome, congenital anomalies, FGR, and perinatal mortality.
- First trimester USS is recommended for suspected multiple gestation to allow for reliable determination of chorionicity or amnionicity.

Early fetal anomaly review

- Awareness of variations in anatomical appearance at different gestational ages is essential to avoid false-positive diagnoses of anomalies. In an unselected, low-risk population, first-trimester sonography can detect 63% of structural abnormalities.
- Although routine screening for fetal development at 11 to 14 weeks is not recommended, offer such screening to women at increased risk of fetal structural and genetic abnormalities.
- Offer NT screening as part of a comprehensive prenatal screening and counselling programme. (NICE CGN 62; 2008)