The First Trimester Screening program

This guide has been designed to highlight the important clinical aspects of using the First Trimester Screening program. It is not intended to teach you all there is to know about First Trimester Screening – it is essential that all those using the program attend a FMF course on First Trimester Screening, have read the FMF 11 – 13^{+6} weeks scan book and have passed the Certificate of Competence in the 11 – 13^{+6} weeks scan. Neither is it designed to tell you how the program works – Astraia have done this in their user guide, setting out the program functions, screen by screen (see Help pages). But it has been written to highlight the new features of this latest version of the program and to make sure the clinicians understand the basis of the risks they are providing.

1. DEMOGRAPHIC DETAILS

Ethnic group

Absence of the fetal nasal bone varies with the ethnic origin of the mother. In addition maternal ethnic group has a major influence on maternal serum biochemistry. Therefore it is important to accurately record the ethnic group of the mother. The lists in the risk calculation are fixed, to ensure that the risks are adjusted appropriately and the mother should be categorised using the following:

- White (European, Middle Eastern, North African, Hispanic)
- Black (African, Caribbean, African American)
- East Asian (Chinese, Japanese, Korean)
- South Asian (Indian, Pakistani, Bangladeshi)
- Mixed (White-Black, White-East Asian, White-South Asian, Black-East Asian, Black-South Asian, East Asian-South Asian)

If any other category is added, the nasal bone and serum biochemistry will not be taken into account for the risk calculation.

Assisted conception

Maternal age and pregnancy dating are often issues complicating risk calculation in IVF pregnancies. Dating in IVF pregnancies is simple as the exact gestational age should be known and there is never an indication to date / redate by CRL. The most accurate way to date an IVF pregnancy is to create an EDD using the date of embryo transfer minus 14 days plus 280 days. The software will now do this automatically if date of embryo transfer is entered.

With regard to maternal age, it is important to know whether the cycle used the mother's own eggs, or those of a donor and whether the eggs were frozen and, if so, for how long. The program will now allow you to put in the correct DOB for the mother, as well as the donor's DOB if you indicate that donor eggs have been used. The risk calculation will then use the donor's age to generate the *a priori* risk. If the exact donor DOB is not known, the software will generate a risk based on the donor's age and assume that she is midway between birthdays. Similarly, the program will correctly adjust the *a priori* risk if the eggs have been frozen. There is no longer a need to adjust the mother's DOB manually to take into account these two factors.

2. FIRST TRIMESTER SCAN

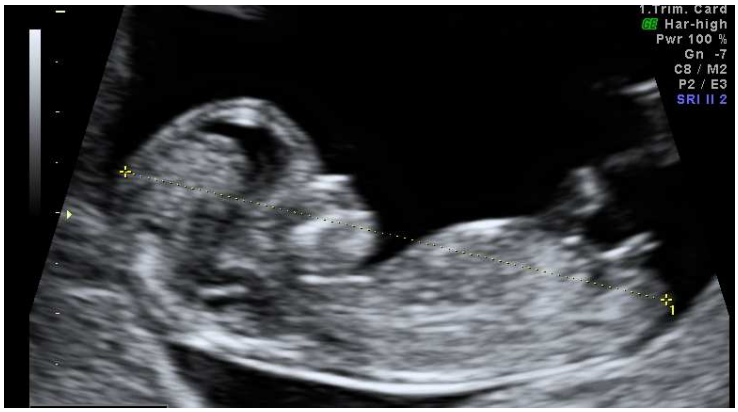
Fetal heart rate

Fetuses with trisomy 21 (T21) have a slight increase in heart rate. However fetuses with trisomy 13 (T13) have a significantly increased heart rate (75% of fetuses with T13 have a FHR > 175 bpm) and the fetal heart rate improves detection of T13. A fetus noted to have a high heart rate should be examined carefully for markers of chromosomal abnormality.

Crown-rump-length

The 11 – 13^{+6} weeks scan can only be performed when the crown-rum-length (CRL) is between 45.0 and 84.0mm. It is very important that the CRL is measured accurately -the algorithm for the calculation of risk using NT includes the CRL measurement and even a small difference in the measurement can have a significant affect on the risk. For example, in a 40 year old woman at 12 weeks with an NT of 2.0mm, if the CRL is measured as 50mm, the risk is 1 in 47, but if the CRL is 70mm, the risk becomes 1 in 254.

The CRL should be measured with the fetus in a neutral position:



Nuchal translucency

When using the FMF risk calculation software, it is essential that the FMF guidelines for the measurement of NT are followed correctly – see appendix 1. An individual will only be given a license to use the risk calculation software if they hold the FMF certificate of competence in the 11 – 13^{+6} weeks scan.

The most important change to the program has been the introduction of the mixture model of NT distributions: The distribution of NT for CRL in both normal and trisomic fetuses follows two distinct patterns:

- In 95% of T21, 70% of T18, 85% of T13 and 5% of chromosomally normal fetuses the fetal NT is high and independent of CRL.
- In 95% of the chromosomally normal group, 5% of T21, 30% of T18 and 15% of T13 there is an identical pattern in NT which increases with CRL.

Fetuses with an increased NT but normal karyotype have a higher incidence of adverse outcome compared with fetuses with a NT measurement within the normal range. Abnormalities include major cardiac defects, musculo-skeletal abnormities, fetal infection and rare genetic syndromes, as well as an increase risk of fetal death. Therefore a detailed anomaly scan, including thorough cardiac evaluation, is recommended for all fetuses with an NT > 95^{th} centile. However, if the karyotype is normal, the increased NT has resolved by 20 weeks and no structural defects are seen, the prognosis is very good and the long term prognosis is similar to that of fetuses with normal NT.

Nuchal cord

A nuchal cord is present in about 5% of pregnancies. The cord has often moved if the patient is scanned later and it does not obviously cause the poor fetal outcome associated with cord accidents. However, it may make the NT difficult to interpret and in this situation the NT must be measured above and below the cord and the average used in the risk calculation. The new software will make this calculation of the mean for you as long as the NT max and NT min are correctly entered when prompted.

Nasal bone

At 11 – 13^{+6} weeks the nasal bone (NB) is not visible by ultrasonography in about 65% of fetuses with T21 and in about 2% of chromosomally normal fetuses. Therefore, the presence of the fetal nasal bone will reduce the risk for T21. There is some ethnic variation in the appearance of the fetal nasal bone, so it is important to correctly attribute maternal ethnic group (see ethnic group section). The software will not use the fetal nasal bone in the risk calculation if the ethnic group is not entered using the grouping provided.

It is essential that the FMF guidelines for the measurement of NB are followed correctly (see appendix 2) and the findings on NB will only be taken into account in the risk assessment if you hold the FMF certificate of competence in NB have the NB included in your license.

When the nasal bone appears to be absent in a patient who otherwise has a low risk result from all other ultrasound markers (with or without serum biochemistry), the FMF advice is that the patient is re-scanned in one week and the risk is only increased at that point if there is persistence of the absence of the nasal bone.

Tricuspid regurgitation

Tricuspid regurgitation (TR) is observed in about 55% of fetuses with T21 and in 1% of chromosomally normal fetuses.

It is essential that the FMF guidelines for assessment of TR are followed correctly (see appendix 3) and the presence or absence of TR will only be taken into account in the risk assessment if you hold the FMF certificate of competence in TR assessment and have the TR included in your license.

TR is associated with cardiac defects and therefore when TR is noted at the 11 – 13^{+6} weeks scan, it is important to carry out a good fetal cardiac examination at 20 – 23 weeks.

Ductus venosus

Blood flow in the ductus venosus (DV) has a characteristic waveform with high velocity during ventricular systole (S-wave) and diastole (a-wave). At 11 – 13^{+6} weeks reversed a-wave in the DV is observed in about 65% of fetuses with T21 and in 3% of chromosomally normal fetuses.

It is essential that the FMF guidelines for the assessment of the DV are followed correctly (see appendix 4) and the DV assessment will only be taken into account in the risk assessment if you hold the FMF certificate of competence in DV assessment and have the DV included in your license.

Reversed a-wave in the DV is associated with cardiac defects and therefore when this pattern is noted at the 11 – 13^{+6} weeks scan, it is important to carry out a good fetal cardiac examination at 20 – 23 weeks.

Fronto-maxillary-facial angle

In fetuses with T21 the flat profile is caused in part by a small maxilla, set back from the other facial bones. This causes an increase in the fronto-maxillary facial angle – the angle is above the 95th centile of the normal range in about 50% of fetuses with T21.

It is essential that the FMF guidelines for the measurement of FMF angle are followed correctly (see appendix 5) and the FMF angle measurement will only be taken into account in the risk assessment if you hold the FMF certificate of competence in FMF angle measurement and have the FMF angle included in your license.

Only the T21 risk is affected by the FMF angle, whereas the risks for T13 and T18, in addition to the T21 risk, are affected by NB, TR and DV.

Major markers

Certain major defects have a very strong association with chromosomal abnormalities and therefore the risk for the typical chromosomal abnormality is fixed irrespective the other ultrasound or biochemical findings.

The major markers include:

- Holoprosencephaly
- Diaphragmatic hernia
- Atrioventricular septal defect
- Exomphalos
- Megacystis

They can be considered in isolation, but the finding of one marker should prompt a very thorough examination of the fetus looking for other markers. The risks are as follows:

Major marker	Fixed risk		
	T21	T18	T13
Holoprosencephaly	-	-	1 in 2
Diaphragmatic hernia	-	1 in 4	-
AVSD	1 in 2	-	-
Exomphalos	-	1 in 4	1 in 10
Megacystis	-	1 in 10	1 in 10
Exomphalos and megacystis	-	1 in 3	1 in 3
Holoprosencephaly and exomphalos / megacystis	-	-	1 in 2
Diaphragmatic hernia and exomphalos / megacystis	-	1 in 2	-

If other ultrasound or biochemical markers are abnormal and the calculated risk is higher than the fixed risk, then the calculated risk will be applied.

<u>Exomphalos</u>
An exomphalos is seen in 1 in 1000 pregnancies between 11 – 13^{+6} weeks. 60% of these will have a chromosomal abnormality, most commonly T18. However care must be taken not to mistake a physiological exomphalos for a pathological one and when the CRL is less than 55mm and an exomphalos containing only bowel is recorded, the following warning message will be displayed:
*Please rescan in one week to confirm because in the majority of cases the exomphalos may resolve. The finding of exomphalos today will not change the risk.*This message does not appear and the risk will be recalculated if it is documented that the exomphalos contains liver.

Megacystis

The fetal bladder can be visualised in 80% of fetuses at 11 weeks and in all cases by 12 weeks. At this gestation the fetal bladder length is usually less than 7mm. The bladder length is 7mm or more in 1 in 1500 pregnancies. In 20% of cases where the bladder length is between 7 and 15mm, there is T13/18, but 90% of those with a normal karyotype resolve spontaneously with good fetal outcome. Conversely those with a bladder length of more than 15mm have only a 10% risk of T13/18, but most go on to develop a progressive obstructive uropathy.

Diaphragmatic hernia

Increased NT thickness is present in about 40% of fetuses with diaphragmatic hernia, including more than 80% of those that result in neonatal death due to pulmonary hypoplasia and in about 20% of the survivors. This suggests that the fetuses with diaphragmatic hernia and increased NT have intrathoracic herniation of the abdominal viscera in the first trimester and prolonged compression of the lungs causes pulmonary hypoplasia.

Minor markers

Minor markers are fetal anomalies of no pathological significance in themselves but are found more commonly in chromosomally abnormal than normal fetuses. They are traditionally considered as second-trimester markers but they can now be seen in the first trimester.

The minor markers considered significant include:

- Choroid plexus cyst (>1.5mm)
- Echogenic intracardiac focus
- hyperechogenic bowel
- hydronephrosis (antero-posterior diameter >1.5mm)

The finding of one or more of these markers should prompt a very thorough scan of the rest of the fetus, looking for other markers of chromosome abnormality. The absence of each marker is reassuring and therefore acts to counterbalance any possible increased risk that the presence of the one marker may have suggested. Therefore it is essential that none of these should be considered in isolation, but as a group and the risk will only be adjusted if this is done. Conversely if no soft markers are found, the risk can be reduced.

Soft markers are only included in the risk calculation for T21 and not for T13/18, although it should be noted that CPCs have a stronger association with T18 rather than T21 and therefore the finding of CPCs should prompt a thorough examination to exclude any other markers of T18.

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Atzei A, Gajewska K, Huggon I, Allan L, Nicolaides KH. Relationship between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. Ultrasound Obstet Gynecol. 2005 Aug;26(2):154-7.

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Sonek J, Borenstein M, Dagklis T, et al. Frontomaxillary facial angle in fetuses with trisomy 21 at 11+ 0 to 13+ 6 weeks. Am J Obstet Gynecol 2007;196;271.e1-4

Sonek J, Borenstein M, Downing C et al. Frontomaxillary facial angles in screening for trisomy 21 at 14-23 weeks' gestation. Am J Obstet Gynecol. 2007 Aug;197(2):160.e1-5

Dagklis T, Plasencia W, Maiz N, Duarte L, Nicolaides KH. Choroid plexus cyst, intracardiac echogenic focus, hyperechogenic bowel and hydronephrosis in screening for trisomy 21 at 11 + 0 to 13 + 6 weeks. Ultrasound Obstet Gynecol. 2008 Feb;31(2):132-5

Liao A, Sebire N, Geerts L, Cicero C, Nicolaides KH. Megacystis at 10-14 weeks of gestation: chromosomal defects and outcome according to bladder length. Ultrasound Obstet Gynecol. 2003 Apr;21(4):338-41

3. MATERNAL SERUM BIOCHEMISTRY

Maternal serum biochemistry can be measured at any time between 8 and 14 weeks. The biochemical markers considered are free beta-hCG and PAPP-A. These markers are influenced by:

- Gestational age
- Maternal weight (in kg)
- Ethnic group (see ethnic group section)
- Smoking (yes / no)
- IVF (yes / no)
- Parity (nulliparous / parous)
- Number of fetuses
- Chorionicity in the case of twins

All these factors significantly affect the MoMs and therefore this information must be accurately entered into the program for valid biochemical assessment. The software will not provide biochemical MoMs (and therefore a risk based on the biochemistry) if any of these data entry fields are not completed.

The biochemical markers used in the first trimester beta-hCG and PAPP-A show the following trends in cases with chromosome abnormalities:

	βhCG	PAPP-A
T21	↑	↓
T18	↓	↓
T13	↓	↓
Triploidy (paternal)	↑↑↑	↓
Triploidy (maternal)	↓↓	↓↓
Sex chromosome abn	→	↓

The gestational age used for the calculation of biochemical risk must be derived from the CRL and is calculated automatically by the software on the basis of the CRL at the time of the 11 – 13^{+6} weeks scan and extrapolated back to the time when the blood was taken if the scan is not performed at the same time as the blood test.

The program will accept biochemical measurements processed by Brahms Kryptor and Delfia Xpress, converting these measurements into MoMs. If any other assay system is used, the MoMs rather than whole values need to be entered, but as the FMF has not certified the laboratory method, it cannot approve the risk (see the Registered laboratories section of the FMF website www.fetalmedicine.com). The software user will see a message on the screening saying that Fetal Medicine Foundation has not approved the biochemical assay used to generate this risk.

Laboratories can manually adjust their medians by 10% if they notice a continuous increase or decrease of their MoM values.

Recent data suggests that pregnancies with low PAPP-A (<0.3MoMs) should be followed up carefully because of poor fetal outcome (fetal growth restriction / preterm delivery / fetal death). The FMF recommends a growth scan at 28 and 32 weeks in addition to their routine antenatal care.

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Spencer K, Kagan K, Nicolaides KH. Screening for trisomy 21 in twin pregnancies in the first trimester: an update of the impact of chorionicity on maternal serum markers. Prenat Diagn. 2008 Jan;28(1):49-52.

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Spencer K, Cowans N, Molina F, Kagan K, Nicolaides KH. First-trimester ultrasound and biochemical markers of aneuploidy and the prediction of preterm or early preterm delivery. Ultrasound Obstet Gynecol. 2008 Feb;31(2):147-52.

4. MULTIPLE PREGNANCIES

Once a twin pregnancy has been recognised, it is essential that the chorionicity is determined based on the presence or absence of the lambda sign. The biochemical markers can be included in the risk calculation but they are affected by chorionicity.

In dating of a multiple pregnancy, the CRL of the largest twin should be used.

In dichorionic twin pregnancies, individual risks will be given for each fetus, based on the findings for that fetus. In monochorionic twin pregnancies (either mono-amniotic or diamniotic) the average risk will be displayed for each fetus. A large (>20%) discrepancy between the nuchal translucency measurements of monochorionic fetuses raises the possibility of early onset severe TTTS.

In multiple pregnancies with more than two fetuses the risk will be based only on ultrasound findings (NT and other markers).

Spencer K, Nicolaides KH. Screening for trisomy 21 in twins using first trimester ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years experience. BJOG. 2003 Mar;110(3):276-80

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Kagan K, Gazzoni A, Sepulveda-Gonzalez G, Sotiriadis A, Nicolaides KH. Discordance in nuchal translucency thickness in the prediction of severe twin-to-twin transfusion syndrome. Ultrasound Obstet Gynecol. 2007 May;29(5):527-32

5. RISKS

The new T21 risk algorithm is built on the idea of contingent screening:

- First-line screening is based on maternal age, fetal NT and serum free beta-hCG & PAPP-A. This will give high-risk results of more than 1 in 50 or low-risk results of less than 1 in 1000 in about 85% of all screened pregnancies.
- In cases where the first-line screening risk is between 1 in 50 and 1 in 1000 the final risk can be adjusted by the inclusion of a series of additional ultrasound markers:
  - Ductus venosus flow
  - Tricuspid flow
  - Nasal bone
  - Fronto-maxillary-facial angle
  - Minor markers

The idea is that these markers need only be taken into account if the risk is equivocal. If the risk after NT and biochemistry is less than 1:1000, then one abnormal new marker will not increase the risk significantly and the patient can be classified as low-risk. If the risk is very high after NT and biochemistry, the risk cannot be improved by the additional markers and the patient is considered as

high-risk. But in the equivocal group, using the additional markers will help to assign them to either a high or low risk group.

The T21 risk is adjusted by (and in the following order):
- Age & gestation adjusted risk +/- previous history of T21
- NT +/- biochemistry
- Additional markers Ductus venosus, Tricuspid blood flow, Nose bone
- Facial angle
- Minor markers
- Major defects

The T18 risk is adjusted by (and in the following order):
- Age & gestation adjusted risk +/- previous history of T21
- NT +/- biochemistry
- Additional markers Ductus venosus, Tricuspid blood flow, Nose bone
- Major defects

The T13 risk is adjusted by (and in the following order):
- Age & gestation adjusted risk +/- previous history of T21
- NT +/- biochemistry
- Additional markers Ductus venosus, Tricuspid blood flow, Nose bone
- Fetal heart rate
- Major defects

The software provides the option of giving the risks at the time of the scan or at term.
Depending on the (national) guidelines centres have the option to switch use of new markers on or off.

Truncation limits
Truncation limits have been applied to the likelihood ratio. In addition the risk is capped if the risk falls outside set limits (1 in 2).

		Maximum risk improvement	Maximum risk increase
NT alone	T21	5x	500x
	T18	3x	500x
	T13	4x	500x
Biochemistry alone	T21, 18 or 13	7x	60x
NT and other USS findings	T21, 18 or 13	20x	1000x
NT and biochemistry alone	T21, 18 or 13	20x	1000x
NT, biochemistry and other USS findings	T21, 18 or 13	33x	1000x

The highest risk that can be given is fixed at 1 in 2.
If the risk based on the NT alone is greater than 1 in 100, then the adjusted risk based on the other ultrasound findings too can only be equal to or higher than the NT only risk. Similarly, if the risk based on the NT and biochemistry is greater than 1 in 50, then the adjusted risk based on the other ultrasound findings too can only be equal to or higher than the NT and biochemistry only risk.

Previously affected pregnancy
In women who have had a previous pregnancy with T21, the risk of recurrence in the subsequent pregnancy is 0.6% higher than the maternal and gestational age-related risk for T21. The possible mechanism for this increased risk is that a small proportion (less than 5%) of couples with a previously affected pregnancy have a parental mosaicism or a genetic defect that interferes with the normal process of dysjunction, so in this group the risk of recurrence is increased substantially. In the majority of couples (more than 95%), the risk of recurrence is not actually increased. The recurrence is

chromosome-specific.

Detection rates

	5% FPR	2% FPR
NT + biochem	92%	
NT + NB, TR, DV, FMF angle + biochem	98%	96%

Risk references:

Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol 1975; 82(9):702-10
[GAD = 8,052 x (CRL+1)^{0,5}+ 23,73]

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6. SCREENING FOR PRE-ECLAMPSIA AND FETAL GROWTH RESTRICTION

Pre-eclampsia (PE) affects about 2% of pregnancies and is a major cause of perinatal and maternal morbidity and mortality. Routine antenatal care has evolved with the aim of identifying women at high-risk for subsequent development of PE and it is well documented that the likelihood of developing PE is increased by a number of factors in the maternal history, including:

ethnic group (Black women have a higher risk of PE)
nulliparity (nulliparous women have a higher risk of PE)
high body mass index (the risk of PE increases with increasing BMI)
history of hypertension (the risk of PE is higher in those with a history of chronic hypertension)
history of pre-eclampsia (the risk of PE is higher in those with a history of PE in a previous pregnancy)

However, screening by maternal history may detect only about 30% of those that will develop PE for a false positive rate of 10%. A more effective method of screening for PE is provided by uterine artery Doppler and measurement of PAPP-A at 11^{+0} to 13^{+6} weeks, in combination with maternal history. At

11^{+0} to 13^{+6} weeks, the uterine artery Doppler PI is higher and the PAPP-A lower in women who will go on to develop PE. For a false-positive rate of 10% the predicted detection rate of early PE (requiring delivery before 34 weeks) is 80%, compared to 40% for late PE. This is particularly important because it is early rather than late PE that is associated with an increased risk of perinatal mortality and morbidity and both short-term and long-term maternal complications.

The FMF software will calculate an individualised risk for PE, based on the maternal history and uterine artery Doppler PI and PAPP-A measured at 11^{+0} to 13^{+6} weeks.

Fetal growth restriction affects 5% of pregnancies and is influenced by a number of maternal and antenatal factors, including the development of PE. The risk of developing fetal growth restriction has also been modelled using a combination of maternal history, uterine artery Doppler PI and the measurement of PAPP-A at 11^{+0} to 13^{+6} weeks. The FMF risk calculation software will calculate this risk too.

It is imperative that, as for the NT scan, sonographers undertaking risk assessment of PE and fetal growth restriction by examination of the uterine arteries must receive appropriate training and certification of their competence (see appendix 6) and the risk calculations are only available to those who hold the FMF certificate of competence in the first trimester assessment of the uterine artery Doppler. In addition, risks will only be provided if all the required demographic fields are completed.

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Spencer K, Cowans NJ, Avgidou K, Molina F, Nicolaides KH. First-trimester biochemical markers of aneuploidy and the prediction of small-for-gestational age fetuses. Ultrasound Obstet Gynecol. 2008 Jan;31(1):15-9

7. SCREENING FOR FETAL DEATH

Reversed a-wave in the ductus venosus is seen in approximately 4% of fetuses at 11^{+0} to 13^{+6} weeks and it is well documented that this abnormal flow pattern is associated with increased risk of chromosomal abnormalities, fetal cardiac defects and fetal death. In the euploid fetus in the second and third trimesters of pregnancy it is well documented that abnormal flow in the ductus is associated with fetal compromise and this appears to be also true in the first trimester. However, in about 80% of cases with a reversed a-wave the pregnancy outcome will be normal.

The flow through the ductus venosus should be observed and documented as either normal or reversed. This finding can then be combined with the other factors providing a significant contribution to the risk of fetal death in a euploid fetus, including:

Maternal ethnic group (risk of fetal death is higher in Black mothers)
Maternal BMI (risk of fetal death increases with increasing BMI)
NT measurement at 11^{+0} to 13^{+6} weeks (risk of fetal death increases with increasing NT)
PAPP-A measurement at 11^{+0} to 13^{+6} weeks (risk of fetal death is higher with a low PAPP-A)

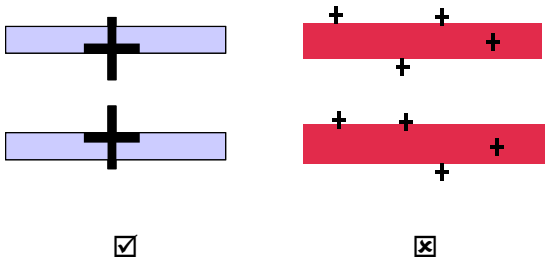
The FMF software will use these factors to calculate a risk of fetal death. However it is essential that all the necessary demographic fields are accurately completed and that the FMF guidelines for the assessment of the DV are followed correctly (see appendix 4). The risk of fetal death will only be taken into account if the required fields completed and you hold the FMF certificate of competence in the measurement of NT and DV assessment and have both included in your license.

Maiz N,, Valencia C, Emmanuel W, Staboulidou I, Nicoliades KH. Screening for adverse pregnancy outcome by Ductus venosus Doppler at 11 to 13+ 6 weeks. Obstet Gynecol 2008 (in press)

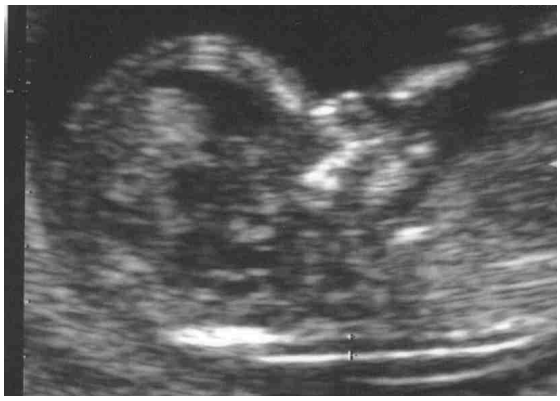
Appendix 1

Protocol for the measurement of nuchal translucency

- The fetal crown-rump length should be between **45 and 84mm**.
- A good **sagittal section** of the fetus must be obtained, with the fetus horizontal on the screen. The correct view is a clearly visualised fetal profile.
- The fetus should be in a **neutral position,** with the head in line with the spine, not hyper-extended or flexed.
- Ideally only the fetal head and upper thorax should be included. The **magnification** should be as large as possible and ALWAYS such that each slight movement of the callipers produces only a 0.1mm change in the measurement.
- The **widest part of translucency** must always be measured.
- Measurements should be taken with the inner border of the horizontal line of the **callipers placed ON the line that defines the nuchal translucency thickness** - the crossbar of the calliper should be such that it is hardly visible as it merges with the white line of the border, not in the nuchal fluid. However, when tissue harmonic imaging (THI) is used the callipers should be placed slightly inside the NT lines rather than on the lines as THI might thicken the lines.



  - In magnifying the image (pre or post freeze zoom) it is important to turn the gain down. This avoids the mistake of placing the calliper on the fuzzy edge of the line which causes an underestimate of the nuchal measurement.
- Care must be taken to **distinguish between fetal skin and amnion**.
- During the scan more than one measurement must be taken and the maximum one that meets all the above criteria should be recorded in the database. It is good practice to retain at least one image for your patient records.



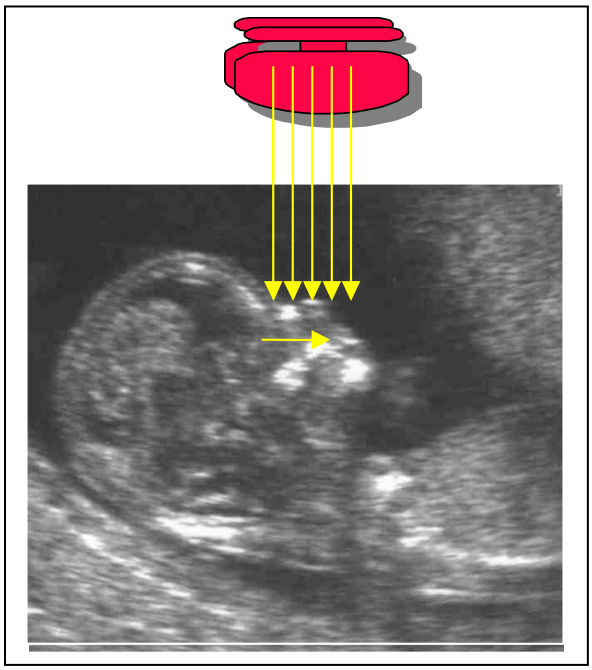
Appendix 2

Protocol for the assessment of fetal nasal bone

1. The gestational period must be 11 to 13^{+6} weeks - the nasal bones first appear at a crown-rump length of 42 mm and increase linearly with gestation.

2. The magnification of the fetus must be such that only the head and upper thorax are present on the screen

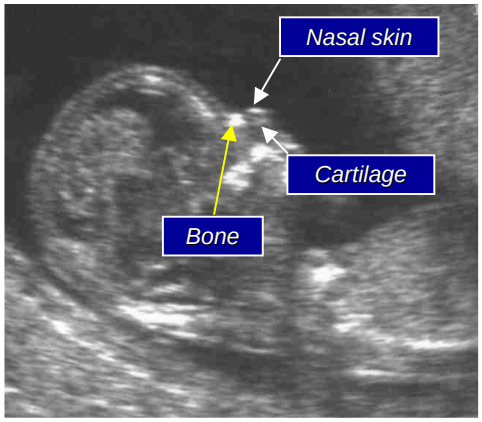
3. A mid-sagittal section of the fetal profile must be obtained with the ultrasound transducer held parallel to the direction of the nose. The ultrasound transducer should be gently tilted from side to side to ensure that the nasal bone is seen separate from the nasal skin.



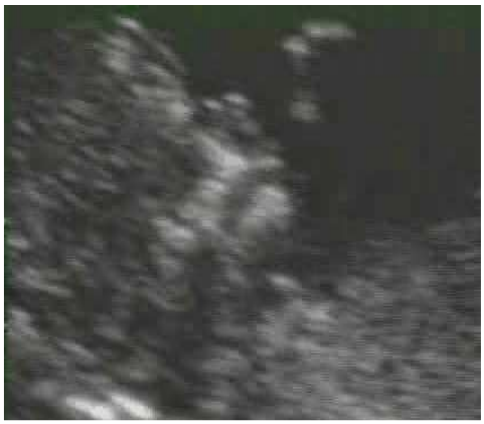
4. The echogenicity of the nasal bone should be greater than the skin overlying it. In this respect, the correct view of the nasal bone should demonstrate three distinct lines:

   - The first two lines, which are proximal to the forehead, are horizontal and parallel to each other, resembling an “equal sign”. The top line represents the skin and the bottom one, which is thicker and more echogenic than the overlying skin, represents the nasal bone.

   - A third line, almost in continuity with the skin, but at a higher level, represents the tip of the nose.



Absence of the bottom line of the equals sign represents the absence of the fetal nasal bone



When the nasal bone line appears as a thin line, less echogenic than the overlying skin, it suggests that the nasal bone is not yet ossified, and it is therefore classified as being absent

Appendix 3

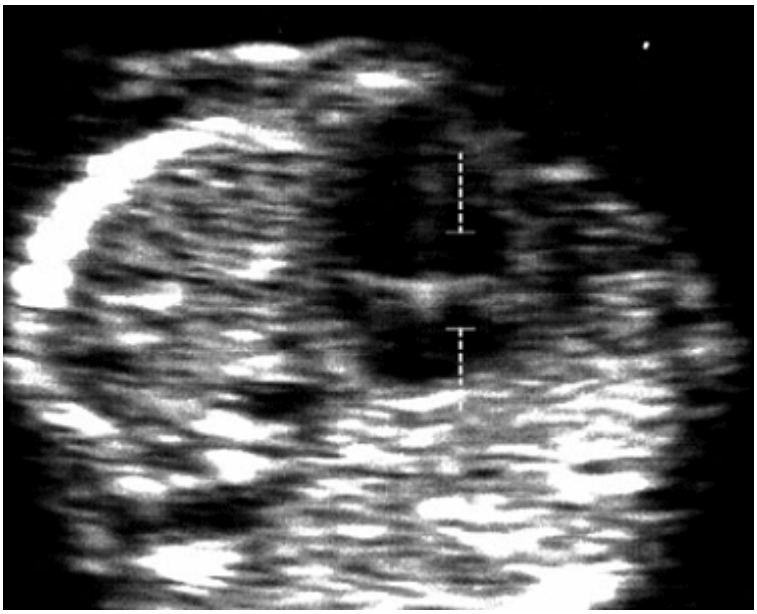
Protocol for the assessment of fetal tricuspid flow

1. The gestational period must be 11 to 13^{+6} weeks

2. The Pulse Repetition Frequency (PRF) should be adjusted to clearly demonstrate the waveform (try -60 to +60). If you detect regurgitation you should increase the scale (try -100 to +100) to ensure that the peaks of the regurgitation do not extend beyond the displayed range.

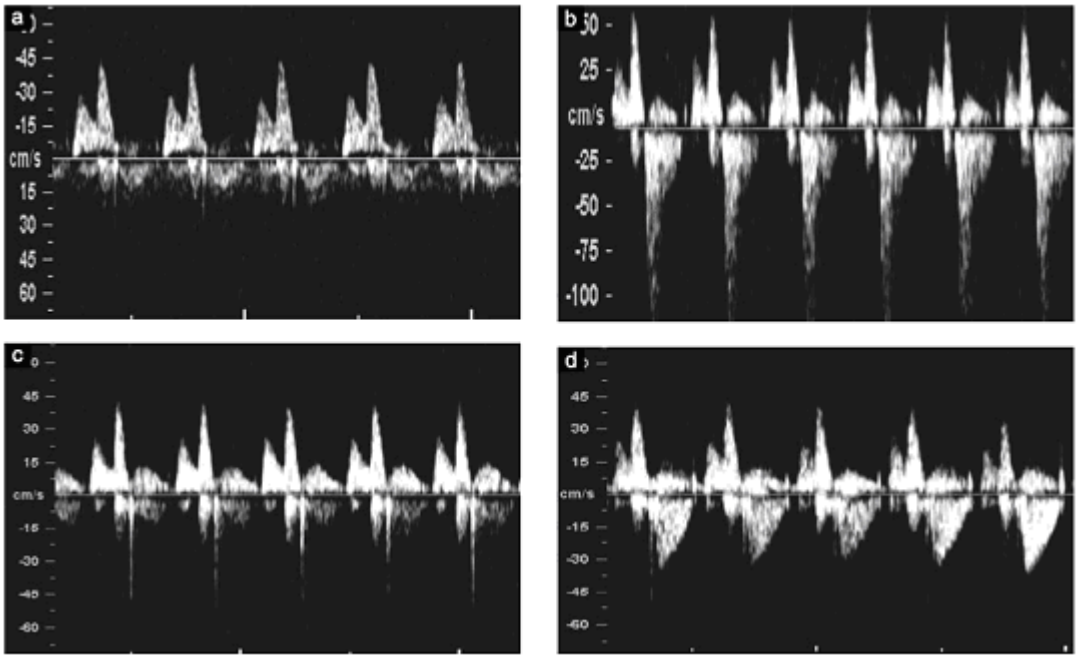
3. An apical four-chamber view of the fetal heart should be obtained

4. A pulsed-wave Doppler sample volume of 2.0 to 3.0 mm should be positioned across the tricuspid valve so that the angle to the direction of flow is less than 30 degrees from the direction of the inter-ventricular septum.



Apical four-chamber view of the heart at 12 weeks. The Doppler sample volume is positioned in the tricuspid valve orifice, including the right atrium and ventricle. The alignment of the atrioventricular valve flow is parallel to the ultrasound beam.

5. Tricuspid regurgitation is diagnosed if it is found during at least half of the systole and with a velocity of over 60 cm/s, since aortic or pulmonary arterial blood flow at this gestation can produce a maximum velocity of 50 cm/s.



Doppler flow profile in the tricuspid valve with no regurgitation during systole (a), and regurgitation during approximately half of systole and with a velocity more than 60 cm/s (b) The short reverse 'spike' generated by closure of the valve cusp (c) and the jet produced by aortic or pulmonary arterial blood flow, which at this gestation can produce a maximum velocity of 50 cm/s (d), should not be mistaken for tricuspid regurgitation.

6. The tricuspid valve could be insufficient in one or more of its three cusps, and therefore the sample volume should be placed across the valve at least three times, in an attempt to interrogate the complete valve.

Appendix 4

Protocol for the assessment of the ductus venosus

1. The gestational period must be 11 to 13^{+6} weeks.

2. The examination should be undertaken during fetal quiescence.

3. The magnification of the image should be such that the fetal thorax and abdomen occupy the whole image.

4. A right ventral mid-sagittal view of the fetal trunk should be obtained and colour flow mapping should be undertaken to demonstrate the umbilical vein, ductus venosus and fetal heart.

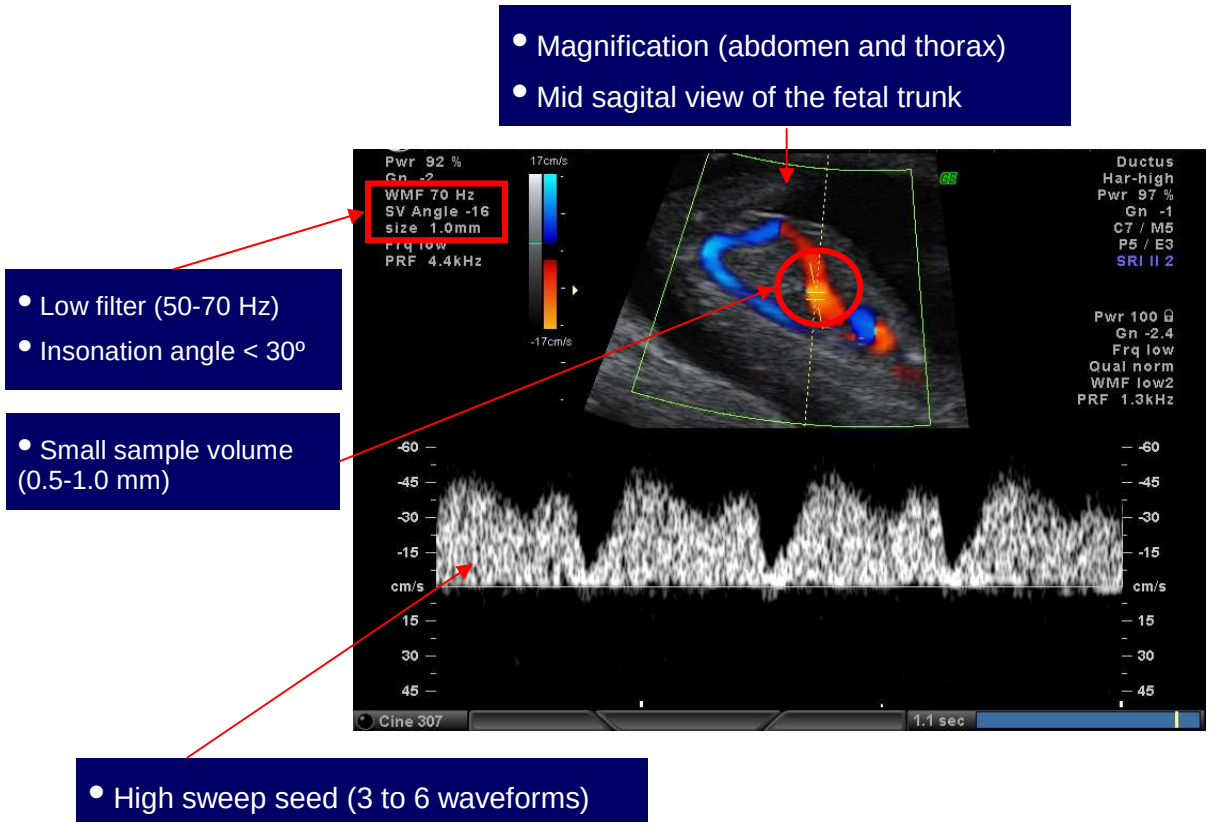
5. The pulsed Doppler sample volume should be small (0.5-1 mm) to avoid contamination from the adjacent veins, and it should be placed in the yellowish aliasing area which is the portion immediately above the umbilical sinus.

6. The insonation angle should be less than 30 degrees.

7. The filter should be set at a low frequency (50-70 Hz) so that the a-wave is not obscured.

8. The sweep speed should be high (2-3 cm/s) so that the waveforms are spread allowing better assessment of the a-wave.

When these criteria are satisfied, it is possible to assess the a-wave and determine qualitatively whether the flow is positive, absent or reversed.



Appendix 5

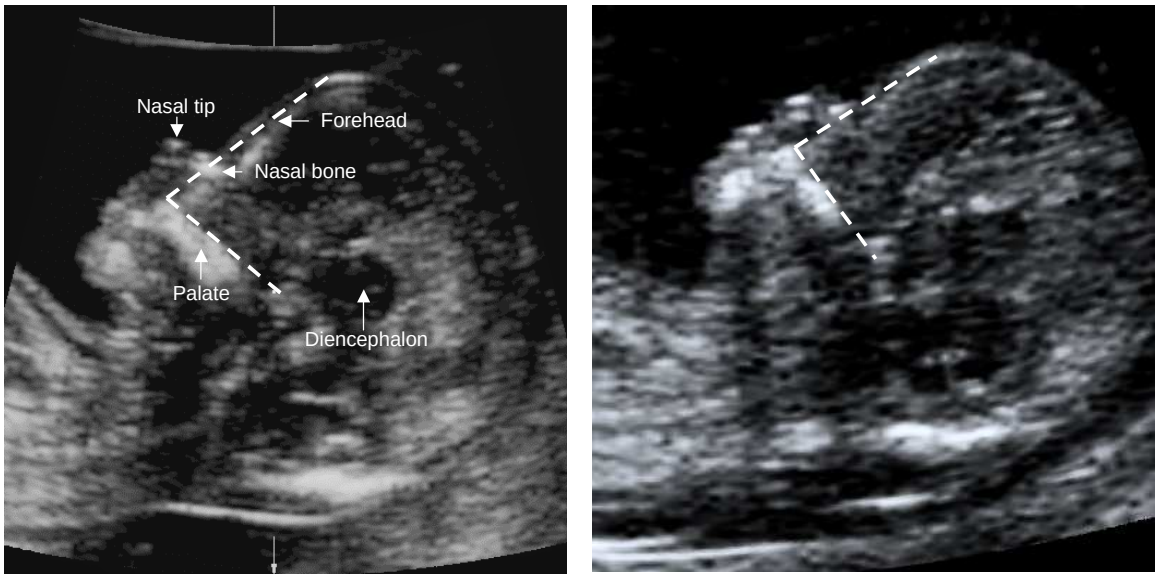
Protocol for the measurement of the facial angle

1. The gestational period must be 11 to 13^{+6} weeks.

2. The magnification of the image should be such that the fetal head and thorax occupy the whole image.

3. A mid-sagittal view of the face should be obtained. This is defined by the presence of the echogenic tip of the nose and rectangular shape of the palate anteriorly, the translucent diencephalon in the centre and the nuchal membrane posteriorly. Minor deviations from the exact midline plane would cause non-visualization of the tip of the nose and visibility of the zygomatic process of the maxilla.

4. The facial angle should be measured between a line along the upper surface of the palate and a line which traverses the upper corner of the anterior aspect of the maxilla extending to the external surface of the forehead, represented by the frontal bones or an echogenic line under the skin below the metopic suture that remains open.



Appendix 6

Protocol for the first-trimester assessment of uterine artery Doppler

1. The gestational age must be 11^{+0} to 13^{+6} weeks.

2. Sagittal section of the uterus must be obtained and the cervical canal and internal cervical os identified. Subsequently, the transducer must be gently tilted from side to side and then colour flow mapping should be used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os.

3. Pulsed wave Doppler should be used with the sampling gate set at 2 mm to cover the whole vessel and ensuring that the angle of insonation is less than 30º. When three similar consecutive waveforms are obtained the PI must be measured and the mean PI of the left and right arteries be calculated.