

ISUOG Practice Guidelines (updated): performance of 11–14-week ultrasound scan

+ B: Clinical Standards Committee

The **International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)** is a scientific organization that encourages sound clinical practice and high-quality teaching and research related to diagnostic imaging in women's healthcare. The ISUOG Clinical Standards Committee (CSC) has a remit to develop Practice Guidelines and Consensus Statements as educational recommendations that provide healthcare practitioners with a consensus-based approach, from experts, for diagnostic imaging. They are intended to reflect what is considered by ISUOG to be the best practice at the time at which they are issued. Although ISUOG has made every effort to ensure that Guidelines are accurate when issued, neither the Society nor any of its employees or members accepts liability for the consequences of any inaccurate or misleading data, opinions or statements issued by the CSC. The ISUOG CSC documents are not intended to establish a legal standard of care, because interpretation of the evidence that underpins the Guidelines may be influenced by individual circumstances, local protocol and available resources. Approved Guidelines can be distributed freely with the permission of ISUOG (info@isuog.org).

+ A: INTRODUCTION

Performing a routine first-trimester ultrasound examination at 11 + 0 to 14 + 0 weeks' gestation is of value for confirming viability and plurality, accurate pregnancy dating, screening for aneuploidies, identification of major structural anomalies and screening for preterm pre-eclampsia. This document aims to provide guidance for healthcare practitioners performing, or planning to perform, pregnancy scans at 11 + 0 to 14 + 0 weeks. Details of the grades of recommendation and levels of evidence used in ISUOG Guidelines are given in Appendix 1.

+ A: GENERAL CONSIDERATIONS

+ B: What is the purpose of a first-trimester ultrasound scan?

In general, the main goal of a pregnancy ultrasound scan is to provide accurate information which will facilitate delivery of optimized antenatal care, ensuring the best possible outcomes for mother and fetus. In early pregnancy, it is important to confirm viability, establish gestational age accurately, determine the number of fetuses and, in the presence of a multiple pregnancy, assess chorionicity and amnionicity. Towards the end of the first trimester, the scan also offers an opportunity to detect major fetal abnormalities and, in healthcare systems that offer first-trimester aneuploidy screening, to measure the **nuchal translucency (NT)** thickness. However, many major malformations may develop later in pregnancy or may not be detected even with appropriate equipment and in the most experienced of hands.

+ B:When should a first-trimester ultrasound scan be performed?

If an earlier first-trimester ultrasound scan has not been done, it is advisable to offer the first scan when gestational age is estimated to be between 11 + 0 and 14 + 0 weeks' gestation, as this provides an opportunity to achieve the aforementioned aims, i.e. confirm viability, establish gestational age accurately, determine the number of viable fetuses and, if requested, evaluate fetal anatomy and risk of aneuploidy¹⁻¹⁸. Before starting the examination, a healthcare provider should counsel the woman/couple regarding the potential benefits and limitations of the first-trimester ultrasound scan (**GOOD PRACTICE POINT**).

+ B:Who should perform the first-trimester ultrasound scan?

Individuals who perform obstetric scans routinely should have specialized training that is appropriate to the practice of diagnostic ultrasound for pregnant women (**GOOD PRACTICE POINT**).

To achieve optimal results from routine ultrasound examinations, it is suggested that scans should be performed by individuals who fulfill the following criteria:

1. have completed training in the use of diagnostic ultrasonography and related safety issues;
2. participate in continuing medical education activities;
3. follow established appropriate care pathways for suspicious or abnormal findings;
4. participate regularly in established quality-assurance programs¹⁹.

+ B:What ultrasonographic equipment should be used?

It is recommended to use equipment that undergoes regular maintenance and servicing and has at least the following capabilities:

- real-time, grayscale two-dimensional (2D) ultrasound;
- color (power) and spectral Doppler;
- M-mode;
- transabdominal ultrasound transducers;
- transvaginal ultrasound transducers;
- adjustable acoustic power output controls with output display standards;
- freeze frame and zoom capabilities;
- electronic calipers;
- capacity to print/store images.

+ B:How should the scan be documented?

An examination report should be produced as an electronic and/or paper document (see Appendix 2 for examples). The document should be stored locally and, in accordance with local protocol, made available to the woman and referring healthcare provider (**GOOD PRACTICE POINT**).

+ B: Is prenatal ultrasonography safe during the first trimester?

There are no indications that the use of B-mode or M-mode prenatal ultrasonography may be harmful during the first trimester, due to their limited acoustic output^{20,21}. However, scanning time should be limited and the lowest possible power output should be used to obtain diagnostic information according to the ALARA (As Low As Reasonably Achievable) principle (**GOOD PRACTICE POINT**).

Doppler ultrasound is, however, associated with greater energy output and, therefore, there are more potential bioeffects, especially when it is applied to a small region of interest and in the embryonic period before 11 weeks' gestation^{20,22,23}. From 11 + 0 to 14 + 0 weeks, spectral Doppler, color flow imaging, power Doppler imaging and other Doppler ultrasound modalities may be used routinely for certain clinical indications, such as screening for aneuploidies and cardiac anomalies. When performing Doppler ultrasound, the displayed thermal index (TI) should be ≤ 1.0 and the exposure time should be kept as short as possible (usually no longer than 5–10 min). Scanning of the maternal uterine arteries (UtA) at any point in the first trimester is unlikely to have any fetal safety implications as long as the embryo/fetus lies outside the Doppler ultrasound beam².

+ B: What if the examination cannot be performed in accordance with these Guidelines?

These Guidelines represent an international benchmark for the first-trimester ultrasound scan, but consideration must be given to local circumstances, protocols and medical practice. If the examination cannot be completed in accordance with these Guidelines, it is advisable to document the reasons for this. In most circumstances, it will be appropriate to repeat the scan, or to refer the case to another healthcare practitioner. This should be done as soon as possible, to minimize unnecessary patient anxiety and any associated delay in achieving the desired goals of the initial examination (**GOOD PRACTICE POINT**).

+ B: What should be done in case of multiple pregnancy?

Determination of chorionicity and amnionicity is important for care, testing and management of multifetal pregnancies. Chorionicity should be determined in early pregnancy, when characterization is most reliable^{24,25}. Once this is accomplished, further antenatal care, including the timing and frequency of ultrasound examinations, should be planned according to the available health resources and ISUOG or local guidelines²⁶ (**GOOD PRACTICE POINT**).

+ A: GUIDELINES FOR EXAMINATION

+ B: 1. Assessment of viability

In early pregnancy, viability is defined by identification of a fetal heartbeat, which is achieved most easily using ultrasound. Fetal cardiac activity can be identified with 2D B-mode ultrasound and the heartbeat can be heard using spectral Doppler. The heart rate, which should be recorded, can be measured using either M-mode or spectral Doppler and is best assessed over a number of cycles. (**GOOD PRACTICE POINT**).

Cardiac activity is typically visible from 5–6 weeks' gestation. Heart rate increases with gestational age up to 10 weeks' gestation (mean, 171 bpm) and then decreases through to 14 + 0 weeks' gestation (mean, 156 bpm)²⁷.

Fetal tachy- or bradycardia may be indicative of aneuploidy or associated with a structural cardiac abnormality^{28,29}. If the fetal heart rate lies outside the normal range, it should be reassessed later in the examination.

+ B: 2. Confirming an intrauterine pregnancy / uterine integrity

Once viability has been demonstrated, it is important to confirm the intrauterine nature of the pregnancy. An intrauterine gestational sac should be bounded completely by myometrium. This is best assessed by performing a sweep covering the entire uterus (**GOOD PRACTICE POINT**).

The integrity of the uterus may be breached when a pregnancy is located in a Cesarean section scar (see section on 'Assessment of risks of obstetric complications') or associated with a rudimentary uterine horn.

+ B: 3. Assessing fetal biometry

There are specific charts for assessing first-trimester fetal biometry³⁸. Systematic measurement of cephalic, abdominal and femoral biometry enables documentation of the presence of essential anatomical landmarks, and abnormalities in measurements can reveal early expression of serious pathologies. However, the cut-off values to be used and the follow-up procedures must be decided in accordance with local protocols, in order to avoid an excessive number of false-positive findings or follow-up examinations.

+ C: Crown–rump length

Crown–rump length (CRL) should be measured as part of the routine first-trimester scan, either transabdominally or transvaginally (Figure 1a). This measurement should be performed, following standard criteria, with the fetus oriented horizontally on the screen so that the measurement line between crown and rump is at about 90° to the ultrasound beam. The fetus should be in a neutral position (i.e. neither flexed nor hyperextended). The image should be magnified to fill most of the width of the ultrasound screen. Calipers should be placed on the end points of the crown and the rump, which need to be visualized clearly^{30,31}. The measurement of CRL should be used to estimate gestational age in all cases except in pregnancies conceived by *in-vitro* fertilization^{32,33}. When multiple CRL measurements have been taken, gestational age should be assessed based on the best-quality CRL measurement between 45 and 84 mm.

A number of different charts have been published and there are small but significant variations in reported measurements for gestational age³⁴. Although older charts are still used widely, it is recommended to use recent, international, prescriptive charts³⁵, because these take into account improvements in image and machine quality and aim to avoid possible statistical bias^{36,37}. The CRL (and not the calculated gestational age) should be used as a gestational reference to define where measurements of NT, UtA Doppler pulsatility index (PI) and biochemical markers free β -human chorionic gonadotropin (β -hCG), pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) lie in relation to the normal range.

The CRL is reduced in fetuses affected by trisomy 18 and triploidy, and care should be taken not to 'normalize' findings by changing dates in fetuses that have obvious structural anomalies. Particular attention should be paid if the CRL is smaller than expected based on an earlier ultrasound measurement.

+ C: Biparietal diameter and head circumference

Biparietal diameter (BPD) and head circumference are measured in the largest symmetrical axial view of the fetal head (Figure 1b). Two techniques for measurement of BPD have been described, placing calipers outer-to-inner (leading edge) or outer-to-outer, perpendicular to the midline falx. Measurements should be made in accordance with the methodology used to establish the nomogram employed.

BPD measurements adjusted for CRL³⁸ and/or abdominal circumference (AC) or transverse abdominal diameter (TAD) may be useful in early screening for myelomeningocele³⁹⁻⁴² and holoprosencephaly⁴³.

+ C: Abdominal circumference

AC is measured in an axial section of the fetal abdomen at the level in which the stomach is visualized (Figure 1c), at the outer surface of the skin line. It is either measured directly with ellipse calipers or calculated from

perpendicular linear measurements, usually the anteroposterior abdominal diameter (APAD) and TAD. To measure APAD, the calipers are placed on the outer borders of the body outline, from the posterior aspect (skin covering the spine) to the anterior abdominal wall. To measure TAD, the calipers are placed on the outer borders of the body outline, across the abdomen at the widest point. AC may be calculated using the formula: $AC = \pi (APAD + TAD)/2 = 1.57 (APAD + TAD)$.

An advantage of performing this measurement is that the image used to record it also shows the stomach in place.

+ C: Femur length

Femur length is measured in the long-axis plane of the femur (Figure 1d). The calipers are placed at either end of the ossified diaphysis, which is clearly visible. An advantage of performing this measurement is that it ensures that the sonographer checks the development of the lower limbs which may reveal early the presence of severe skeletal anomalies⁴⁴.

+ B: 4. Assessment of fetal anatomy

A significant proportion of structural anomalies can be detected through detailed systematic examination of fetal anatomy at 11 + 0 to 14 + 0 weeks' gestation⁴⁵⁻⁴⁷. These anomalies will be detected reliably only if:

- examination of the structure is included in the protocol for routine assessment;
- adequate time is allocated for a detailed structural survey.

Successful early detection of fetal structural anomalies is also dependent on the standard of equipment available for screening, the skill set of the sonographers and sonologists and the prevalence of the anomalies in the population. Some sonographic features of structural abnormality have been described only relatively recently, and it is not yet clear how these markers perform in population screening. We therefore describe two levels of screening, presenting both a checklist of 'minimum requirements' for a basic structural survey at 11 + 0 to 14 + 0 weeks' gestation (Table 1) and a more advanced level of 'best practice' for comprehensive detailed examination of the fetus in the first trimester (Table 2). There is currently limited evidence describing the health economic benefit of early identification of fetal structural abnormalities.

+ C: Basic examination with minimum requirements for scanning a fetus at 11 + 0 to 14 + 0 weeks

The 11 + 0 to 14 + 0-week scan provides an opportunity to assess fetal anatomy and should not be limited to assessment of fetal CRL and NT. Whilst cell-free (cf) DNA provides a highly effective means of screening for common aneuploidies, this test cannot identify structural defects, which may be associated with a more extensive range of rarer chromosomal abnormalities. Identification of a structural abnormality may support an invasive rather than a non-invasive approach to testing for aneuploidy⁴⁸⁻⁵⁰. Several severe structural anomalies can be detected in almost all cases⁴⁹ and their presence or absence should be assessed as a minimum standard in all patients presenting for an 11 + 0 to 14 + 0-week scan (**GOOD PRACTICE POINT**).

+ C: Detailed assessment of fetal anatomy at 11 + 0 to 14 + 0-week scan

Most structural anomalies occur in pregnancies categorized as being at 'low risk' by traditional (history-based) approaches to screening. Effective detection of structural anomalies therefore relies on routine examination of the whole population rather than examination of predefined risk groups only. Demonstration of normal anatomy at 11 + 1 to 14 + 0 weeks provides early reassurance for most pregnant women. Early identification of a major anomaly allows earlier genetic diagnosis and more time for parental counseling and decision-making.

Detailed assessment of fetal anatomy at 11 + 0 to 14 + 0 weeks is best achieved using high-resolution transabdominal and transvaginal transducers. Both transabdominal and transvaginal approaches may be required to complete a systematic examination of fetal organs and adequate time needs to be scheduled for this assessment. While a transvaginal examination is not mandatory, it may provide better image resolution for the assessment of fetal anatomy, especially in women with increased body mass index, uterine fibroids and/or retroverted uterus. Within this 3-week time interval, the fetus almost doubles in size (CRL, 45–84 mm). Visualization of many anatomical details by ultrasound is best achieved at around 13 weeks' gestation (**GOOD PRACTICE POINT**).

Several studies have shown that the adoption of a systematic examination including a standardized protocol is associated with a significant increase in the detection rate of anomalies in early gestation^{46,47,51,52}. As sonographers and sonologists gain more experience in screening at 11 + 0 to 14 + 0 weeks, changing from a protocol based on 'minimum requirements' to a more extensive 'best-practice' systematic review will allow detection of a higher proportion and a wider range of structural anomalies.

A systematic approach to detailed assessment of the fetal anatomy at 11 + 0 to 14 + 0 weeks should include the following (Table 2).

Overview of fetus, placenta and uterus. An overview of the fetus should be assessed (Figure 2a). The placenta should appear as slightly echogenic, with uniform, homogeneous echotexture, without small or large cysts or lacunae (Figure 2b). The presence or absence of a subchorionic hematoma should be assessed. Prediction of the

final placental location in relation to the internal cervical os can be challenging in the first trimester and subject to false-positive reporting of low-lying placenta. However, in a patient with a history of a previous Cesarean section, a careful assessment of the placenta could help in the early detection of an abnormal invasive placenta. This is discussed in the section on ‘Assessment of risks of obstetric complications’. Within the uterus, the presence or absence of fibroids, amniotic bands and synechiae should be evaluated.

Amniotic fluid and membranes. Amniotic fluid in early gestation is rarely reduced or increased as observed in the second-trimester scan, and cannot be used as a hint for anomalies. The amniotic membranes are often well visualized as a sac surrounding the fetus and not yet fused with the chorion. When there is a history of bleeding, a blood clot is often identified in the retroamniotic space. In multiple pregnancy, chorionicity and amnionicity should be determined and documented (Figure 2c).

Head and brain. Examination of the fetal head and central nervous system is best achieved using a combination of axial and midsagittal planes. The axial plane is used to visualize ossification of the skull and the symmetry of the developing brain structures. Cranial bone ossification should be visible by 11 completed gestational weeks. The cerebral region is dominated by lateral ventricles that appear large and are almost filled in their posterior two thirds with the slightly asymmetric echogenic choroid plexuses (Figure 2d). The hemispheres appear symmetrical and are separated by the interhemispheric fissure and falx. The brain mantle is very thin and best appreciated anteriorly, lining the large fluid-filled ventricles (Figure 2e). A lower plane within the head shows the two thalami and the posterior fossa region with the cerebral peduncles and the aqueduct of Sylvius, the fourth ventricle and the future cisterna magna as fluid-filled structures (Figure 2f).

A midsagittal plane of the head / face can also be used to assess the posterior fossa and visualize the intracranial translucency (fourth ventricle) and brainstem as a screening test for open neural tube defects and cystic posterior fossa malformations (Figure 2g).

Fetal face. Visualization of the fetal face is best achieved in the midsagittal plane, which should be complemented with examination in either an axial or a coronal plane. The magnified midsagittal plane of the head and neck enables assessment of several anatomic regions of the face, including the forehead, nasal bone, maxilla, mandible and mouth (Figure 2g). Different facial angles and markers (e.g. maxillary gap, superimposed line-sign) have been proposed to assess the presence of facial clefts in the midsagittal view but these need confirmation in other planes^{33,34}. In an axial or coronal view an attempt should be made to visualize the eyes with their interorbital distance and the retronasal triangle, demonstrating the maxilla and the mandible (Figure 2h and 2i). The nasal bone is ‘absent’ or hypoplastic in 50–60% of fetuses with trisomy 21 and this can be used as an additional marker to improve efficacy of ultrasound-based screening.

Neck. Sonographic assessment and measurement of NT should be part of the screening protocol (Figure 1e), independent of whether it is used for risk assessment for aneuploidy. Increased NT may be a marker for rarer aneuploidies in pregnancies, while cfDNA has been used mostly to screen for a more limited range of common aneuploidies. The standardized method for measurement of NT is reviewed in the aneuploidy section of these Guidelines. Other discrete fluid-filled collections may be seen in the sides of the neck and are associated with dilated jugular lymph sacs and cystic hygroma.

NT is increased in up to 40% of fetuses that have a major cardiac abnormality and is associated with other structural and genetic anomalies and an increased risk of intrauterine fetal death^{55,56}.

Thorax and heart. The thoracic cavity with lungs and heart are evaluated in the fetal four-chamber plane (Figure 2j). In this plane, the ribs, lungs, situs and cardiac position in the chest are assessed, with the cardiac axis pointing to the left (the normal axis is at 30–60°)^{57,58}. The lungs should appear homogeneously echogenic, and there should be no sign of pleural effusion. Diaphragmatic continuity is evaluated in an axial, sagittal/parasagittal or coronal plane, noting normal intra-abdominal position of the stomach and liver. Early assessment of the fetal heart is achieved more reliably by combining grayscale with color Doppler imaging. Color Doppler helps to confirm the presence of two distinct ventricles with separate filling in diastole and to exclude significant atrioventricular valve regurgitation (Figure 2k). Examination of the great vessels through identification of the left ventricular outflow tract and three-vessels-and-trachea view with color Doppler demonstrates the presence, number and size of the great vessels, their anatomic relationship and the direction of blood flow, along with the continuity of the ductal and aortic arches, enabling ruling out of most complex anomalies affecting the great vessels (Figure 2l). Multicenter studies have shown better detection rates of cardiac anomaly when using multiple planes in addition to the use of color Doppler⁵⁹.

Abdominal content. The stomach and bladder are the only echolucent fluid-filled structures in the abdomen and pelvis. The position of the stomach on the left side of the abdomen, together with levocardia, help confirm normal visceral situs (Figure 2m). The fetal kidneys can often be seen in their expected paraspinal location as bean-shaped, slightly echogenic structures, with typical hypoechoic central renal pelvis (Figure 2r). By 12 weeks' gestation, the fetal bladder should be visible as a median hypoechoic round structure in the lower abdomen, with a longitudinal diameter < 7 mm (Figure 2p and 2q).

Abdominal wall. The normal insertion of the umbilical cord should be documented after 12 weeks (Figure 2n). Physiologic midgut herniation is present up to 11 weeks and should be differentiated from omphalocele and gastroschisis.

Umbilical cord. The number of cord vessels and the cord insertion at the umbilicus should be noted. Brief evaluation of the paravesical region with color or power Doppler can be helpful in confirming the presence of two umbilical arteries (Figure 2o). **Single umbilical artery (SUA)** does not constitute an anomaly, but is associated with congenital anomalies and fetal growth restriction. Care should be taken not to cause anxiety to the parents when SUA is detected, if no major anomaly is found at the first-trimester scan. There is, as yet, no consensus regarding the potential impact of SUA on pregnancy outcome. Placental cord insertion can also be assessed reliably at this stage with color Doppler.

Spine. The spine should be examined, when possible, in a sagittal view, to assess vertebral alignment and integrity of skin covering (Figure 2s). Vertebral bodies are ossified after 12 weeks' gestation. Particular attention should be paid to the appearance of the spine when any intracranial signs suspicious for open spina bifida are found⁶.

Limbs. Presence of the three segments of both upper and lower limbs and presence and normal orientation of the two hands and feet should be noted at the 11 + 0 to 14 + 0-week ultrasound scan (Figure 2t and 2u).

Genitalia. Evaluation of the external genitalia and fetal sex is based upon the orientation of the genital tubercle in the sagittal plane (Figure 2q).

*Role of **three-dimensional (3D)** and 4D ultrasound.* 3D and 4D ultrasound are not currently used for routine first-trimester fetal anatomical evaluation. However, in experienced hands, these methods may be helpful in evaluation of abnormalities, especially with multiplanar reconstruction of selected diagnostic planes.

+ B: 5. Assessing risk for common forms of aneuploidy (trisomies 21, 18 and 13)

+ C: Pretest counseling

Women should be made aware and consent to screening for common aneuploidies before such an assessment is carried out. This requires:

- specification of conditions for which testing is being carried out, and those for which it is not;
- clarification of the differences between screening and diagnostic testing;
- identification of patient-specific factors that will impact on the appropriateness of a test;
- discussion of baseline levels of risk based on maternal age and family history;
- shared decision-making;
- explanation of how test results will be communicated after the test;
- discussion of the various screening and diagnostic options and of their merits and limitations.

+ C: Ultrasound-based assessment at 11 + 0 to 14 + 0 weeks' gestation

There are two common tests used to screen for common aneuploidies: combined first-trimester screening (includes risks derived from maternal history, ultrasound and maternal serum biochemistry); and cfDNA testing (also known as **non-invasive prenatal testing (NIPT)** or **non-invasive prenatal screening (NIPS)**). Combined first-trimester screening tests for common trisomies, which comprise approximately 50% of all genetic aberrations identifiable prenatally by array-based genomic assessment. Combined first-trimester screening is also effective to diagnose Turner syndrome. cfDNA testing may be extended to include other aneuploidies, including microdeletions and microduplications. The range of conditions for which testing is carried out is dependent on the test provider.

Most clinicians using combined first-trimester screening to calculate risks for the common aneuploidies, i.e. trisomies 21, 18 and 13, use a risk algorithm that is freely available from The Fetal Medicine Foundation^{61,62}. The basic algorithm combines an *a-priori* risk based on maternal age, gestational age and maternal history of previous pregnancy with trisomy 21, 18 or 13 with ultrasound measurement of NT thickness and assessment of maternal serum free β -hCG and PAPP-A^{63,64}. The *a-priori* risk is altered by multiplying it by a likelihood ratio derived for each of these factors. Likelihood ratios are calculated by comparing frequency distributions for each specific marker in chromosomally normal and abnormal populations.

+ C: Nuchal translucency thickness

The term NT describes the echolucent region seen at the back of the fetal neck during sonographic assessment. NT should be measured in the midsagittal section (Figure 1e), using an image that:

- has been magnified to include the head and thorax of the fetus only;
- is magnified such that calipers measure 0.1-mm increments;
- allows assessment of the entire length of the nuchal region and measurement at its maximum thickness;
- demonstrates the fetus in a neutral position (extension or flexion of the neck affect measurement);
- demonstrates the fetus separate from the amnion to ensure the appropriate space is measured.

The NT is measured with 'square' calipers placed on its echogenic margins. Three measurements should be made (on separate images) and the largest is used for risk assessment.

The correct, standardized technique for NT measurement has been described by Nicolaides⁶⁵. As this measurement is used to calculate a likelihood ratio for risk calculation, accurate assessment is essential. This is achieved by restricting performance of NT measurement to trained personnel who agree to undergo

a continuous process of quality assurance that compares reported measures to a recognized international standard. Some quality-assurance programs are run nationally; others allow sonographers to participate internationally (www.fetalmedicine.org).

+ C: First-trimester biochemistry

First-trimester screening efficacy is improved by combining ultrasound-based NT measurement with assessment of maternal free β -hCG and PAPP-A. Most national guidelines recommend combining these markers when screening for trisomies 21, 18 and 13. These markers show different patterns of up- or down-regulation in the three common trisomies, which enables individualized risk assessment for each of these aneuploidies.

Recently, data have demonstrated that low maternal serum concentrations of PlGF at 11 + 0 to 14 + 0 weeks' gestation are associated with common trisomies, suggesting that PlGF can be incorporated within the risk calculation, especially when it has already been measured in screening for preterm pre-eclampsia (see section on 'Assessment of risks of obstetric complications').

+ C: Additional ultrasound markers

Nasal bone. Several other ultrasound markers for aneuploidy have been described. Delayed ossification of the nasal bone, reported as 'hypoplastic' or 'absence of the' nasal bone at 11 + 0 to 14 + 0 weeks' gestation, is a powerful marker in screening for trisomy 21. The nasal bone is rarely 'hypoplastic' or 'absent' in euploid fetuses and consequently this dichotomized variable is associated with large positive and negative likelihood ratios⁶⁶⁻⁶⁹. This potentially allows significant improvement in specificity whilst maintaining high sensitivity⁶⁹.

The nasal bone is assessed in the same midsagittal section as NT, with a magnified image that includes the echogenic tip of the nose and the rectangular shape of the palate anteriorly. Posterior to it, and centrally in the brain, the translucent diencephalon and the nuchal membrane can be identified. The nasal bone lies below the echogenic skin line of the face. The nasal bone should normally be more echogenic than the skin at the tip and the bridge of the nose, which lies immediately above the bone itself (Figure 1e)⁶⁷. If the nasal bone cannot be demonstrated to be more echogenic than the skin above, then it is deemed hypoplastic or absent.

Ductus venosus flow (Figure 1f). Fetuses affected by aneuploidy are more likely to have structural or functional cardiac defects at 11 + 0 to 14 + 0 weeks' gestation. Functional anomalies include abnormal flow in the ductus venosus and tricuspid regurgitation.

Initial studies demonstrated an association between reversal of the ductus venosus A-wave^{70,71}, but more recent studies showed that an increase in ductus venosus **pulsatility index for veins (PIV)** was associated with an increased risk for common trisomies. The latter ultrasound marker can be used as a continuous variable, with less significant changes in likelihood ratios, thus allowing easier incorporation into a screening program⁷¹⁻⁷³.

The ductus venosus is normally assessed in a right paramedial section. Color Doppler is used to identify flow returning through the umbilical vein and ductus venosus to the right atrium. A 1-mm pulsed-wave Doppler gate can be used to demonstrate the waveform, which has a typical appearance (Figure 1f)⁷⁰. The PIV is measured by autotracing.

Tricuspid flow (Figure 1g). Flow through the tricuspid valve is assessed by identifying the four-chamber view in an axial section of the thorax and placing the ultrasound transducer so that the apex of the heart appears at either a 12 o'clock or a 6 o'clock position. A 2–4-mm pulsed-wave gate is placed across the anterior semilunar valve (the tricuspid valve) and used to interrogate the waveform (Figure 1g). Tricuspid regurgitation is defined as flow > 60 cm/s for > 50% of the cardiac cycle⁷⁴. This dichotomous variable is rarely abnormal in euploid fetuses and is associated with high positive and negative likelihood ratios^{75,76}.

Screening performance. The mixture model⁶³ proposed by The Fetal Medicine Foundation (and made freely available) has been assessed prospectively and found to have 90% sensitivity for 97% specificity when screening for trisomy 21⁷⁷. Similar screening efficacy for trisomy 21 was reported in a second, national, screening program⁷⁸. The Fetal Medicine Foundation has also reported the effectiveness of screening for a wider range of chromosomal abnormalities in a study including > 100000 pregnancies. At a specificity of 96%, the detection rate for trisomy 21 was 90%, that for trisomy 18 was 97%, that for trisomy 13 was 92% and that for Turner syndrome was > 95%⁶² (**LEVEL OF EVIDENCE: IIc**).

Whilst inclusion of other markers may improve screening efficacy and, most significantly, specificity, these ultrasound markers require additional skills for reliable assessment and there is the potential to reduce screening efficacy if they are applied poorly. As a consequence, in clinical practice, many examiners continue to use a combination of NT thickness and the biochemical markers free β -hCG and PAPP-A.

Screening for trisomy 21 and other common trisomies has evolved over the years in an attempt to increase the detection rate and reduce the false positive rate. In recent years, screening by cfDNA has been demonstrated to achieve excellent performance for common aneuploidies. For trisomy 21, the cfDNA test

can detect 99.7% of cases at a 0.04% false-positive rate; for trisomy 18, it can detect 97.9% of cases at a 0.04% false-positive rate; and for trisomy 13, it can detect 99.0% of cases at a 0.04% false-positive rate⁹. Currently, the cfDNA test has been introduced as second-tier screening, following first-trimester combined screening (**LEVEL OF EVIDENCE: Ib**). It is not recommended as a standalone test without performance of the 11 + 0 to 14 + 0-week scan.

Different screening algorithms are available and the choice will depend on the available resources^{62,71,80-82} (Table 3). The different screening strategies are explained and detection rates and false-positive rates are reported based on available studies.

Post-test counseling. During post-test counseling, the result(s) should be provided and the ongoing risk interpreted for the patient. If a screening test describes an ‘increased chance’ then the likelihood of the pregnancy being truly affected (positive predictive value) should be discussed. Counseling should include:

- discussing the options for further testing, including benefits and limitations and risks associated with invasive procedures;
- establishing whether the individual wishes to proceed with further testing;
- ensuring that other health professionals involved in managing the pregnancy are aware of the tests that have been performed and their results.

+ B: 6. Assessment of risks of obstetric complications

+ C: Scar pregnancy and placental abnormalities

The echostructure of the placenta should be evaluated. Abnormal findings, such as masses, single or multiple cystic spaces or large subchorionic fluid collection (> 5 cm), should be noted and followed up. The position of the placenta in relation to the cervix is of less importance at this stage of pregnancy, since most placentas are not low-lying until the mid trimester⁸³. Placenta previa should not be reported at this stage (**GOOD PRACTICE POINT**).

Special attention should be paid to the increasing number of patients with a prior Cesarean delivery, who may be predisposed to scar pregnancy or placenta accreta spectrum (PAS) disorders, with significant complications⁸⁴. Prenatal diagnosis of these placental anomalies at any gestational age is associated with improved maternal outcome, by allowing treatment in centers with expertise in surgical management. Moreover, early first-trimester diagnosis of Cesarean scar pregnancy is associated with a lower risk of adverse maternal outcome⁸⁵. Therefore, some authors have recently proposed that a policy of early (5–7

weeks) transvaginal ultrasound screening of women with a prior Cesarean delivery would predict reliably the ultrasound stage of a PAS disorder^{85,86}. However, these Guidelines refer only to a ‘standard’ late first-trimester ultrasound examination, i.e. performed at 11 + 0 to 14 + 0 weeks, and do not address the issue of very early scans. At 11 + 0 to 14 + 0 weeks, ultrasound signs suggestive of PAS disorders can be detected^{84,87-90}. Low anterior implantation of the placenta/gestational sac, next to or in the scar niche, is the most common early ultrasound sign associated with PAS disorders (Figure 3a). Depending on local resources, this may be sought using transvaginal ultrasound at the time of the late first-trimester scan in women with prior Cesarean delivery. A finding of placental implantation over an exposed scar predicts the risk of PAS with an excellent negative predictive value⁸⁹.

In the first trimester, women who are likely to give birth prematurely tend to have a shorter cervix compared with those who will give birth at term⁹¹⁻⁹³. First- and second-trimester cervical-length measurements correlate⁹⁴. Measurement of the cervix in the first trimester (Figure 3b), possibly in combination with personal history, could identify a group at increased risk of preterm birth⁹⁵. However, it has not yet been proven that measuring the cervix in the first trimester improves outcome. Such an approach needs to be fully standardized and more data should be obtained before this can be recommended routinely^{95,96}.

Gynecological pathology, both benign and malignant, may be detected during any first-trimester scan. Abnormalities of uterine shape, such as uterine septa and bicornuate uteri, should be described. The adnexa should be surveyed for abnormalities and masses. The relevance and management of such findings are beyond the scope of these Guidelines.

+ C: Screening for pre-eclampsia at 11 + 0 to 14 + 0-week scan

There is a substantial body of evidence to support risk-based screening for preterm pre-eclampsia using various biomarkers. The most established approach to screening, namely, the first-trimester combined test for pre-eclampsia, combines the *a-priori* risk from maternal characteristics and medical history (Table 4) with measurement of UtA-PI, serum PIGF and mean arterial pressure (MAP)⁹⁷⁻⁹⁹. This method of screening has been validated prospectively in countries within and beyond Europe¹⁰⁰⁻¹⁰³.

Pregnant women with singleton pregnancy attending for the 11 + 0 to 14 + 0-week scan should be offered screening for preterm pre-eclampsia by the first-trimester combined test, involving maternal factors (Table 4) and biomarkers, as a one-step procedure. The risk calculator is available free of charge at <https://fetalmedicine.org/research/assess/pre-eclampsia>. The best combined test is one that includes maternal factors and measurements of UtA-PI, PIGF and MAP¹⁰⁴, with a cut-off of ≥ 1 in 100^{104,105} (**LEVEL OF EVIDENCE: Ib**).

The UtA-PI should be measured during the same transabdominal scan as that for measurement of fetal NT thickness and diagnosis of major fetal defects at 11 + 0 to 14 + 0 weeks' gestation (corresponding to fetal CRL of 45–84 mm). Gestational age must be determined from the fetal CRL measurement (see section on 'Assessing fetal biometry'). During this scan, a sagittal section of the uterus is obtained and the cervical canal and internal cervical os are identified. Then, keeping the transducer in the midline and tilting it gently to the sides, with the use of color flow mapping, each UtA is identified along the side of the cervix and uterus, at the level of the internal os (Figure 1h). Pulsed-wave Doppler is used, with a sampling gate of 2 mm to cover the whole vessel, and care is taken to ensure that the angle of insonation is $< 30^\circ$. When three similar consecutive waveforms have been obtained, the UtA-PI is measured with automatic tracing and the mean PI of the left and right UtAs is calculated^{105,106}. The measurement of UtA-PI must be carried out by sonographers who have received appropriate training and accreditation, such as that provided by The Fetal Medicine Foundation (www.fetalmedicine.org).

When it is not possible to measure UtA-PI and/or PIGF, the baseline screening test should be a combination of maternal factors with MAP, not maternal factors alone. If maternal serum PAPP-A is measured for routine first-trimester screening for fetal aneuploidies (see section on 'Assessing risk for common forms of aneuploidy (trisomies 21, 18 and 13)'), this result can be included for pre-eclampsia risk assessment. Variations of the full combined test, e.g. combining maternal factors with UtA-PI and MAP, would lead to a reduction in the screening performance¹⁰⁴.

An alternative, if resources are limited, is routine screening for preterm pre-eclampsia by maternal factors and MAP in all pregnancies, reserving measurements of UtA-PI and PIGF for a subgroup of the population selected on the basis of the risk derived from screening by maternal factors and MAP alone¹⁰⁷ (**GOOD PRACTICE POINT**).

Following first-trimester screening for preterm pre-eclampsia, women identified as being at high risk should receive aspirin prophylaxis commencing between 11 and 15 + 6 weeks' gestation at a dose of 150 mg to be taken every night until either 36 weeks' gestation, when delivery occurs or when pre-eclampsia is diagnosed¹⁰⁸. Such low-dose aspirin should not be prescribed to all pregnant women. In women with low calcium intake (< 800 mg/day), either calcium replacement (≥ 1 g elemental calcium/day) or calcium supplementation (1.5–2 g elemental calcium/day) may reduce the rates of both preterm and term pre-eclampsia¹⁰⁹.

+ A: GUIDELINE AUTHORS*

C. M. Bilardo, Departments of Obstetrics and Fetal Medicine, Amsterdam UMC, Amsterdam, The Netherlands

R. Chaoui, Center for Prenatal Diagnosis and Human Genetics, Berlin, Germany

J. A. Hyett, Western Sydney University, Sydney, Australia

K. O. Kagan, Department of Obstetrics and Gynecology, University of Tuebingen, Tuebingen, Germany

J. N. Karim, Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, UK

K. H. Nicolaides, Fetal Medicine Research Institute, King's College Hospital, London, UK

A. T. Papageorgiou, Fetal Medicine Unit, St George's University of London, London, UK

L. C. Poon, Department of Obstetrics and Gynaecology, Chinese University of Hong Kong, Hong Kong SAR, China

L. J. Salomon, Department of Obstetrics and Fetal Medicine, Paris Cité University, Assistance Publique-Hopitaux de Paris, Hopital Necker Enfants Malades, Paris, France

A. Syngelaki, Fetal Medicine Research Institute, King's College Hospital, London, UK

*Arranged alphabetically.

+ A: CITATION

These Guidelines should be cited as: 'International Society of Ultrasound in Obstetrics and Gynecology, Bilardo CM, Chaoui R, Hyett JA, Kagan KO, Karim JN, Papageorgiou AT, Poon LC, Salomon LJ, Syngelaki A, Nicolaides KH. ISUOG Practice Guidelines (updated): performance of 11–14-week ultrasound scan. *Ultrasound Obstet Gynecol* 2023; **61**: xxx–xxx.'

+ A: REFERENCES

1. Whitworth M, Bricker L, Mullan C. Ultrasound for fetal assessment in early pregnancy. *Cochrane Database Syst Rev* 2015; **7**: CD007058.
2. Bennett KA, Crane JMG, O'Shea P, Lacelle J, Hutchens D, Copel JA. First trimester ultrasound screening is effective in reducing postterm labor induction rates: a randomized controlled trial. *Am J Obstet Gynecol* 2004; **190**: 1077–1081.
3. Hoffman CS, Messer LC, Mendola P, Savitz DA, Herring AH, Hartmann KE. Comparison of gestational age at birth based on last menstrual period and ultrasound during the first trimester. *Paediatr Perinat Epidemiol* 2008; **22**: 587–596.
4. Taipale P, Hiilesmaa V. Predicting delivery date by ultrasound and last menstrual period in early gestation. *Obstet Gynecol* 2001; **97**: 189–194.
5. Skalkidou A, Kieler H, Stephansson O, Roos N, Cnattinguis S, Haglund B. Ultrasound pregnancy dating leads to biased perinatal morbidity and neonatal mortality among post-term-born girls. *Epidemiology* 2010; **21**: 791–796.

6. Harrington D, MacKenzie I, Thompson K, Fleminger M, Greenwood C. Does a first trimester dating scan using crown rump length measurement reduce the rate of induction of labour for prolonged pregnancy? An uncompleted randomised controlled trial of 463 women. *BJOG* 2006; **113**: 171–176.
7. Ott WJ. Accurate gestational dating: revisited. *Am J Perinatol* 1994; **11**: 404–408.
8. Wisser J, Dirschedl P, Krone S. Estimation of gestational age by transvaginal sonographic measurement of greatest embryonic length in dated human embryos. *Ultrasound Obstetrics Gynecol* 1994; **4**: 457–462.
9. Tunon K, Eik-Nes S, Grøttum P, Von Düring V, Kahn J. Gestational age in pregnancies conceived after in vitro fertilization: a comparison between age assessed from oocyte retrieval, crown–rump length and biparietal diameter. *Ultrasound Obstet Gynecol* 2000; **15**: 41–46.
10. Grange G, Pannier E, Goffinet F, Cabrol D, Zorn J-R. Dating biometry during the first trimester: accuracy of an every-day practice. *Eur J Obstet Gynecol Reprod Biol* 2000; **88**: 61–64.
11. Chalouhi G, Bernard J, Benoist G, Nasr B, Ville Y, Salomon LJ. A comparison of first trimester measurements for prediction of delivery date. *J Matern Fetal Neonatal Med* 2011; **24**: 51–57.
12. Salomon LJ, Pizzi C, Gasparrini A, Bernard J-P, Ville Y. Prediction of the date of delivery based on first trimester ultrasound measurements: an independent method from estimated date of conception. *J Matern Fetal Neonatal Med* 2010; **23**: 1–9.
13. Caughey AB, Nicholson JM, Washington AE. First- vs second-trimester ultrasound: the effect on pregnancy dating and perinatal outcomes. *Am J Obstet Gynecol* 2008; **198**: 703.e1–6.
14. Thorsell M, Kaijser M, Almström H, Andolf E. Expected day of delivery from ultrasound dating versus last menstrual period—obstetric outcome when dates mismatch. *BJOG* 2008; **115**: 585–589.
15. Bottomley C, Bourne T. Dating and growth in the first trimester. *Best Pract Res Clin Obstet Gynaecol* 2009; **23**: 439–452.
16. Sonek J. First trimester ultrasonography in screening and detection of fetal anomalies. *Am J Med Genet C Semin Med Genet* 2007; **145C**: 45–61.
17. Snijders R, Johnson S, Sebire N, Noble P, Nicolaides KH. First-trimester ultrasound screening for chromosomal defects. *Ultrasound Obstet Gynecol* 1996; **7**: 216–226.
18. Bromley B, Henningsen C, Jones D, Timor-Tritsch I, Simpson L, Thiel L. AIUM practice parameter for the performance of detailed diagnostic obstetric ultrasound examinations between 12 weeks 0 days and 13 weeks 6 days. *J Ultrasound Med* 2021; **40**: E1–16.
19. Ville Y. ‘Ceci n’est pas une échographie’: a plea for quality assessment in prenatal ultrasound. *Ultrasound Obstet Gynecol* 2008; **31**: 1–5.
20. Salvesen K, Abramowicz J, Ter Haar G, Miloro P, Sinkovskaya E, Dall'Asta A, Maršál K, Lees C. ISUOG statement on the safe use of Doppler for fetal ultrasound examination in the first 13 + 6 weeks of pregnancy (updated). *Ultrasound Obstet Gynecol* 2021; **57**: 1020.
21. Torloni MR, Vedmedovska N, Merialdi M, Betrán A, Allen T, González R, Platt L. Safety of ultrasonography in pregnancy: WHO systematic review of the literature and meta-analysis. *Ultrasound Obstet Gynecol* 2009; **33**: 599–608.
22. Abramowicz J, Kossoff G, Marsal K, Ter Haar G. International Society of Ultrasound in Obstetrics and Gynecology Bioeffects and Safety Committee. Executive Board of the International Society of Ultrasound in

Obstetrics and Gynecology. Safety Statement, 2000 (reconfirmed 2003). International Society of Ultrasound in Obstetrics and Gynecology (ISUOG). *Ultrasound Obstet Gynecol* 2003; **21**: 100.

23. HersHKovitz R, Sheiner E, Mazor M. Ultrasound in obstetrics: a review of safety. *Eur J Obstet Gynecol Reprod Biol* 2002; **101**: 15–18.

24. Lewi L, Jani J, Blickstein I, Huber A, Gucciardo L, Van Mieghem T, Doné E, Boes A-S, Hecher K, Gratacós E. The outcome of monochorionic diamniotic twin gestations in the era of invasive fetal therapy: a prospective cohort study. *Am J Obstet Gynecol* 2008; **199**: 514.e1–8.

25. Dias T, Arcangeli T, Bhide A, Napolitano R, Mahsud-Dornan S, Thilaganathan B. First-trimester ultrasound determination of chorionicity in twin pregnancy. *Ultrasound Obstet Gynecol* 2011; **38**: 530–532.

26. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, Kilby MD, Lewi L, Nicolaides KH, Oepkes D. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. *Ultrasound Obstet Gynecol* 2016; **47**: 247–263.

27. Hyett J, Noble P, Snijders R, Montenegro N, Nicolaides KH. Fetal heart rate in trisomy 21 and other chromosomal abnormalities at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol* 1996; **7**: 239–244.

28. Liao A, Snijders R, Geerts L, Spencer K, Nicolaides KH. Fetal heart rate in chromosomally abnormal fetuses. *Ultrasound Obstet Gynecol* 2000; **16**: 610–613.

29. Baschat A, Gembruch U, Knöpfle G, Hansmann M. First-trimester fetal heart block: a marker for cardiac anomaly. *Ultrasound Obstet Gynecol* 1999; **14**: 311–314.

30. Dhombres F, Roux N, Friszer S, Bessis R, Khoshnood B, Jouannic J-M. Relation between the quality of the ultrasound image acquisition and the precision of the measurement of the crown-rump length in the late first trimester: what are the consequences? *Eur J Obstet Gynecol Reprod Biol* 2016; **207**: 37–44.

31. Wanyonyi S, Napolitano R, Ohuma E, Salomon L, Papageorghiou A. Image-scoring system for crown–rump length measurement. *Ultrasound Obstet Gynecol* 2014; **44**: 649–654.

32. Savitz DA, Terry Jr JW, Dole N, Thorp Jr JM, Siega-Riz AM, Herring AH. Comparison of pregnancy dating by last menstrual period, ultrasound scanning, and their combination. *Am J Obstet Gynecol* 2002; **187**: 1660–1666.

33. Salomon L, Alfírevic Z, Da Silva Costa F, Deter R, Figueras F, Ghi Ta, Glanc P, Khalil A, Lee W, Napolitano R. ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth. *Ultrasound Obstet Gynecol* 2019; **53**: 715–723.

34. Napolitano R, Dhami J, Ohuma EO, Ioannou C, Conde-Agudelo A, Kennedy SH, Villar J, Papageorghiou AT. Pregnancy dating by fetal crown–rump length: a systematic review of charts. *BJOG* 2014; **121**: 556–565.

35. Papageorghiou A, Kennedy S, Salomon L, Ohuma E, Cheikh Ismail L, Barros F, Lambert A, Carvalho M, Jaffer Y, Bertino E. International standards for early fetal size and pregnancy dating based on ultrasound measurement of crown–rump length in the first trimester of pregnancy. *Ultrasound Obstet Gynecol* 2014; **44**: 641–648.

36. Ohuma EO, Papageorghiou AT, Villar J, Altman DG. Estimation of gestational age in early pregnancy from crown-rump length when gestational age range is truncated: the case study of the INTERGROWTH-21st Project. *BMC Med Res Methodol* 2013; **13**: 1–14.

37. Økland I, Bjåstad T, Johansen T, Gjessing H, Grøttum P, Eik-Nes S. Narrowed beam width in newer ultrasound machines shortens measurements in the lateral direction: fetal measurement charts may be obsolete. *Ultrasound Obstet Gynecol* 2011; **38**: 82–87.

38. Salomon LJ, Bernard JP, Duyme M, Dorion A, Ville Y. Revisiting first-trimester fetal biometry. *Ultrasound Obstet Gynecol* 2003; **22**: 63–66.

39. Suresh S, Sudarshan S, Rangaraj A, Indrani S, Cuckle H. Spina bifida screening in the first trimester using ultrasound biparietal diameter measurement adjusted for crown-rump length or abdominal circumference. *Prenat Diagn* 2019; **39**: 314–318.
40. Simon EG, Arthuis CJ, Haddad G, Bertrand P, Perrotin F. Biparietal/transverse abdominal diameter ratio \leq 1: potential marker for open spina bifida at 11–13-week scan. *Ultrasound Obstet Gynecol* 2015; **45**: 267–272.
41. Bernard J-P, Cuckle HS, Bernard MA, Brochet C, Salomon LJ, Ville Y. Combined screening for open spina bifida at 11–13 weeks using fetal biparietal diameter and maternal serum markers. *Am J Obstet Gynecol* 2013; **209**: 223.e1–5.
42. Karl K, Benoit B, Entezami M, Heling KS, Chaoui R. Small biparietal diameter in fetuses with spina bifida on 11–13-week and mid-gestation ultrasound. *Ultrasound Obstet Gynecol* 2012; **40**: 140–144.
43. Sepulveda W, Wong AE, Andreeva E, Odegova N, Martinez-Ten P, Meagher S. Biparietal Diameter-to-Crown-Rump Length Disproportion in First-Trimester Fetuses With Holoprosencephaly. *J Ultrasound Med* 2014; **33**: 1165–1169.
44. Khalil A, Pajkrt E, Chitty LS. Early prenatal diagnosis of skeletal anomalies. *Prenat Diagn* 2011; **31**: 115–124.
45. Syngelaki A, Chelemen T, Dagklis T, Allan L, Nicolaides KH. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks. *Prenat Diagn* 2011; **31**: 90–102.
46. Syngelaki A, Hammami A, Bower S, Zidere V, Akolekar R, Nicolaides KH. Diagnosis of fetal non-chromosomal abnormalities on routine ultrasound examination at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2019; **54**: 468–476.
47. Karim JN, Roberts NW, Salomon LJ, Papageorgiou AT. Systematic review of first trimester ultrasound screening in detecting fetal structural anomalies and factors affecting screening performance. *Ultrasound Obstet Gynecol* 2017; **50**: 429–441.
48. Syngelaki A, Guerra L, Ceccacci I, Efeturk T, Nicolaides KH. Impact of holoprosencephaly, exomphalos, megacystis and increased nuchal translucency on first-trimester screening for chromosomal abnormalities. *Ultrasound Obstet Gynecol* 2017; **50**: 45–48.
49. Benachi A, Letourneau A, Kleinfinger P, Senat M-V, Gautier E, Favre R, Bidat L, Houfflin-Debauge V, Bouyer J, Costa J-M. Cell-free DNA analysis in maternal plasma in cases of fetal abnormalities detected on ultrasound examination. *Obstet Gynecol* 2015; **125**: 1330–1337.
50. Srebniak MI, de Wit MC, Diderich KE, Govaerts LC, Joosten M, Knapen MF, Bos MJ, Looye-Bruinsma GA, Koningen M, Go AT. Enlarged NT (≥ 3.5 mm) in the first trimester—not all chromosome aberrations can be detected by NIPT. *Mol Cytogenet* 2016; **9**: 1–7.
51. Kenkhuis M, Bakker M, Bardi F, Fontanella F, Bakker M, Fleurke-Rozema J, Bilardo C. Effectiveness of 12–13-week scan for early diagnosis of fetal congenital anomalies in the cell-free DNA era. *Ultrasound Obstet Gynecol* 2018; **51**: 463–469.
52. Liao Y, Wen H, Ouyang S, Yuan Y, Bi J, Guan Y, Fu Q, Yang X, Guo W, Huang Y. Routine first-trimester ultrasound screening using a standardized anatomical protocol. *Am J Obstet Gynecol* 2021; **224**: 396.e1–5.
53. Chaoui R, Orosz G, Heling KS, Sarut-Lopez A, Nicolaides KH. Maxillary gap at 11–13 weeks' gestation: marker of cleft lip and palate. *Ultrasound Obstet Gynecol* 2015; **46**: 665–669.

54. Lakshmy S, Rose N, Masilamani P, Umapathy S, Ziyauulla T. Absent 'superimposed-line' sign: novel marker in early diagnosis of cleft of fetal secondary palate. *Ultrasound Obstet Gynecol* 2020; **56**: 906–915.
55. Souka AP, Snijders RJ, Novakov A, Soares W, Nicolaides KH. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol* 1998; **11**: 391–400.
56. Bilardo C, Müller M, Pajkrt E, Clur S, Van Zalen M, Bijlsma E. Increased nuchal translucency thickness and normal karyotype: time for parental reassurance. *Ultrasound Obstet Gynecol* 2007; **30**: 11–18.
57. Sinkovskaya E, Horton S, Berkley EM, Cooper JK, Indika S, Abuhamad A. Defining the fetal cardiac axis between 11 + 0 and 14 + 6 weeks of gestation: experience with 100 consecutive pregnancies. *Ultrasound Obstet Gynecol* 2010; **36**: 676–681.
58. Sinkovskaya ES, Chaoui R, Karl K, Andreeva E, Zhuchenko L, Abuhamad AZ. Fetal cardiac axis and congenital heart defects in early gestation. *Obstet Gynecol* 2015; **125**: 453–460.
59. Karim JN, Bradburn E, Roberts N, Papageorghiou AT, ACCEPTS study. First-trimester ultrasound detection of fetal heart anomalies: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2022; **59**: 11–25.
60. Chaoui R, Benoit B, Mitkowska-Wozniak H, Heling KS, Nicolaides KH. Assessment of intracranial translucency (IT) in the detection of spina bifida at the 11–13-week scan. *Ultrasound Obstet Gynecol* 2009; **34**: 249–252.
61. Kagan KO, Wright D, Baker A, Sahota D, Nicolaides KH. Screening for trisomy 21 by maternal age, fetal nuchal translucency thickness, free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. *Ultrasound Obstet Gynecol* 2008; **31**: 618–624.
62. Santorum M, Wright D, Syngelaki A, Karagiotti N, Nicolaides KH. Accuracy of first-trimester combined test in screening for trisomies 21, 18 and 13. *Ultrasound Obstet Gynecol* 2017; **49**: 714–720.
63. Wright D, Kagan KO, Molina FS, Gazzoni A, Nicolaides KH. A mixture model of nuchal translucency thickness in screening for chromosomal defects. *Ultrasound Obstet Gynecol* 2008; **31**: 376–383.
64. Kagan KO, Wright D, Spencer K, Molina FS, Nicolaides KH. First-trimester screening for trisomy 21 by free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A: impact of maternal and pregnancy characteristics. *Ultrasound Obstet Gynecol* 2008; **31**: 493–502.
65. Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. *Am J Obstet Gynecol* 2004; **191**: 45–67.
66. Cicero S, Rembouskos G, Vandecruys H, Hogg M, Nicolaides KH. Likelihood ratio for trisomy 21 in fetuses with absent nasal bone at the 11–14-week scan. *Ultrasound Obstet Gynecol* 2004; **23**: 218–223.
67. Cicero S, Curcio P, Papageorghiou A, Sonek J, Nicolaides KH. Absence of nasal bone in fetuses with trisomy 21 at 11–14 weeks of gestation: an observational study. *Lancet* 2001; **358**: 1665–1667.
68. Cicero S, Avgidou K, Rembouskos G, Kagan KO, Nicolaides KH. Nasal bone in first-trimester screening for trisomy 21. *Am J Obstet Gynecol* 2006; **195**: 109–114.
69. Kagan KO, Cicero S, Staboulidou I, Wright D, Nicolaides KH. Fetal nasal bone in screening for trisomies 21, 18 and 13 and Turner syndrome at 11–13 weeks of gestation. *Ultrasound Obstet Gynecol* 2009; **33**: 259–264.
70. Matias A, Gomes C, Flack N, Montenegro N, Nicolaides KH. Screening for chromosomal abnormalities at 10–14 weeks: the role of ductus venosus blood flow. *Ultrasound Obstet Gynecol* 1998; **12**: 380–384.

71. Maiz N, Valencia C, Kagan KO, Wright D, Nicolaides KH. Ductus venosus Doppler in screening for trisomies 21, 18 and 13 and Turner syndrome at 11–13 weeks of gestation. *Ultrasound Obstet Gynecol* 2009; **33**: 512–517.
72. Timmerman E, Oude Rengerink K, Pajkrt E, Opmeer BC, van der Post JAM, Bilardo CM. Ductus venosus pulsatility index measurement reduces the false-positive rate in first-trimester screening. *Ultrasound Obstet Gynecol* 2010; **36**: 661–667.
73. Wagner P, Sonek J, Klein J, Hoopmann M, Abele H, Kagan KO. First-trimester ultrasound screening for trisomy 21 based on maternal age, fetal nuchal translucency, and different methods of ductus venosus assessment. *Prenat Diagn* 2017; **37**: 680–685.
74. Huggon IC, DeFigueiredo DB, Allan LD. Tricuspid regurgitation in the diagnosis of chromosomal anomalies in the fetus at 11–14 weeks of gestation. *Heart* 2003; **89**: 1071–1073.
75. Falcon O, Auer M, Gero-vassili A, Spencer K, Nicolaides KH. Screening for trisomy 21 by fetal tricuspid regurgitation, nuchal translucency and maternal serum free beta-hCG and PAPP-A at 11 + 0 to 13 + 6 weeks. *Ultrasound Obstet Gynecol* 2006; **27**: 151–155.
76. Kagan KO, Valencia C, Livanos P, Wright D, Nicolaides KH. Tricuspid regurgitation in screening for trisomies 21, 18 and 13 and Turner syndrome at 11 + 0 to 13 + 6 weeks of gestation. *Ultrasound Obstet Gynecol* 2009; **33**: 18–22.
77. Kagan KO, Etchegaray A, Zhou Y, Wright D, Nicolaides KH. Prospective validation of first-trimester combined screening for trisomy 21. *Ultrasound Obstet Gynecol* 2009; **34**: 14–18.
78. Ekelund CK, Jorgensen FS, Petersen OB, Sundberg K, Tabor A, Danish Fetal Medicine Research Group. Impact of a new national screening policy for Down's syndrome in Denmark: population based cohort study. *BMJ* 2008; **337**: a2547.
79. Gil M, Accurti V, Santacruz B, Plana M, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. *Ultrasound Obstet Gynecol* 2017; **50**: 302–314.
80. Kagan KO, Sroka F, Sonek J, Abele H, Lüthgens K, Schmid M, Wagner P, Brucker S, Wallwiener D, Hoopmann M. First-trimester risk assessment based on ultrasound and cell-free DNA vs combined screening: a randomized controlled trial. *Ultrasound Obstet Gynecol* 2018; **51**: 437–444.
81. Prodan NC, Wiechers C, Geipel A, Walter A, Siegmann HJ, Kozłowski P, Hoopmann M, Kagan KO. Universal Cell Free DNA or Contingent Screening for Trisomy 21: Does It Make a Difference? A Comparative Study with Real Data. *Fetal Diagn Ther* 2022; **49**: 85–94.
82. Miltoft C, Rode L, Ekelund C, Sundberg K, Kjaergaard S, Zingenberg H, Tabor A. Contingent first-trimester screening for aneuploidies with cell-free DNA in a Danish clinical setting. *Ultrasound Obstet Gynecol* 2018; **51**: 470–479.
83. Mustafa S, Brizot M, Carvalho M, Watanabe L, Kahhale S, Zugaib M. Transvaginal ultrasonography in predicting placenta previa at delivery: a longitudinal study. *Ultrasound Obstet Gynecol* 2002; **20**: 356–359.
84. D'Antonio F, Timor-Tritsch I, Palacios-Jaraquemada J, Monteagudo A, Buca D, Forlani F, Minneci G, Foti F, Manzoli L, Liberati M. First-trimester detection of abnormally invasive placenta in high-risk women: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2018; **51**: 176–183.
85. Timor-Tritsch I, Buca D, Di Mascio D, Cali G, D'Amico A, Monteagudo A, Tinari S, Morlando M, Nappi L, Greco P. Outcome of cesarean scar pregnancy according to gestational age at diagnosis: A systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 2021; **258**: 53–59.

86. Calí G, Timor-Tritsch I, Forlani F, Palacios-Jaraquemada J, Monteagudo A, Agten AK, Flacco M, Khalil A, Buca D, Manzoli L. Value of first-trimester ultrasound in prediction of third-trimester sonographic stage of placenta accreta spectrum disorder and surgical outcome. *Ultrasound Obstet Gynecol* 2020; **55**: 450–459.
87. Doulaveris G, Ryken K, Papathomas D, Trejo FE, Fazzari MJ, Rotenberg O, Stone J, Roman AS. Early prediction of placenta accreta spectrum in women with prior cesarean delivery using transvaginal ultrasound at 11 to 14 weeks. *Am J Obstet Gynecol MFM* 2020; **2**: 100183.
88. Panaiotova J, Tokunaka M, Krajewska K, Zosmer N, Nicolaides KH. Screening for morbidly adherent placenta in early pregnancy. *Ultrasound Obstet Gynecol* 2019; **53**: 101–106.
89. Bhatia A, Palacio M, Wright A, Yeo G. Lower uterine segment scar assessment at 11–14 weeks' gestation to screen for placenta accreta spectrum in women with prior Cesarean delivery. *Ultrasound Obstet Gynecol* 2022; **59**: 40–48.
90. Stirnemann JJ, Mousty E, Chalouhi G, Salomon LJ, Bernard J-P, Ville Y. Screening for placenta accreta at 11–14 weeks of gestation. *Am J Obstet Gynecol* 2011; **205**: 547.e1–6.
91. Greco E, Gupta R, Syngelaki A, Poon LC, Nicolaides KH. First-trimester screening for spontaneous preterm delivery with maternal characteristics and cervical length. *Fetal Diagn Ther* 2012; **31**: 154–161.
92. Wulff CB, Rode L, Rosthøj S, Hoseth E, Petersen O, Tabor A. Transvaginal sonographic cervical length in first and second trimesters in a low-risk population: a prospective study. *Ultrasound Obstet Gynecol* 2018; **51**: 604–613.
93. Souka AP, Papastefanou I, Michalitsi V, Salambasis K, Chrelias C, Salamalekis G, Kassanos D. Cervical length changes from the first to second trimester of pregnancy, and prediction of preterm birth by first-trimester sonographic cervical measurement. *J Ultrasound Med* 2011; **30**: 997–1002.
94. Souka A, Papastefanou I, Michalitsi V, Papadopoulos G, Kassanos D. A predictive model of short cervix at 20–24 weeks using first-trimester cervical length measurement and maternal history. *Prenat Diagn* 2011; **31**: 202–206.
95. Kuleva M, Castaing O, Fries N, Bernard J-P, Bussi eres L, Fontanges M, Moeglin D, Salomon LJ. A standardized approach for the assessment of the lower uterine segment at first trimester by transvaginal ultrasound: a flash study. *J Matern Fetal Neonatal Med* 2016; **29**: 1376–1381.
96. Retzke J, Sonek J, Lehmann J, Yazdi B, Kagan K. Comparison of three methods of cervical measurement in the first trimester: 11 + 0 to 14 + 0-line, two-line, and tracing. *Prenat Diagn* 2013; **33**: 262–268.
97. Wright D, Akolekar R, Syngelaki A, Poon LC, Nicolaides KH. A competing risks model in early screening for preeclampsia. *Fetal Diagn Ther* 2012; **32**: 171–178.
98. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther* 2013; **33**: 8–15.
99. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol* 2015; **213**: 62.e1–10.
100. Tan M, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, Singh M, Greco E, Wright A, Maclagan K. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstet Gynecol* 2018; **51**: 743–750.
101. Skr  stad R, Hov G, Blaas HG, Romundstad P, Salvesen K. Risk assessment for preeclampsia in nulliparous women at 11–13 weeks gestational age: prospective evaluation of two algorithms. *BJOG* 2015; **122**: 1781–1788.

102. Guizani M, Valsamis J, Dutemeyer V, Kang X, Ceccotti V, Khalife J, Duiella SF, Blavier F, Faraca A, Cos T. First-trimester combined multimarker prospective study for the detection of pregnancies at a high risk of developing preeclampsia using the Fetal Medicine Foundation-algorithm. *Fetal Diagn Ther* 2018; **43**: 266–273.
103. Park FJ, Leung CH, Poon LC, Williams PF, Rothwell SJ, Hyett JA. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. *Aust N Z J Obstet Gynaecol* 2013; **53**: 532–539.
104. Tan MY, Syngelaki A, Poon LC, Rolnik DL, O’Gorman N, Delgado JL, Akolekar R, Konstantinidou L, Tsavdaridou M, Galeva S. Screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks’ gestation. *Ultrasound Obstet Gynecol* 2018; **52**: 186–195.
105. Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc P, Khalil A, Martins W, Odibo A, Papageorgiou A, Salomon L. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. *Ultrasound Obstet Gynecol* 2019; **53**: 7–22.
106. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2007; **30**: 742–749.
107. Wright D, Gallo D, Gil Pugliese S, Casanova C, Nicolaides KH. Contingent screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol* 2016; **47**: 554–559.
108. Rolnik DL, Wright D, Poon LC, O’Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017; **377**: 613–622.
109. Hofmeyr GJ, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2018; **10**: CD001059.

+ A: APPENDICES

Appendix 1 Grades of recommendation and levels of evidence used in ISUOG Guidelines

Classification of evidence levels	
1 ++	High-quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with very low risk of bias
1 +	Well-conducted meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with low risk of bias
1–	Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with high risk of bias
2 ++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with very low risk of confounding, bias or chance and high probability that the relationship is causal
2 +	Well-conducted case–control or cohort studies with low risk of confounding, bias or chance and moderate probability that the relationship is causal
2–	Case–control or cohort studies with high risk of confounding, bias or chance and significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

<i>Grades of recommendation</i>	
A	At least one meta-analysis, systematic review or randomized controlled trial rated as 1 ++ and applicable directly to the target population; or a systematic review of randomized controlled trials or a body of evidence consisting principally of studies rated as 1 + applicable directly to the target population and demonstrating overall consistency of results
B	Body of evidence including studies rated as 2 ++ applicable directly to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1 ++ or 1 +
C	Body of evidence including studies rated as 2 + applicable directly to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2 ++
D	Evidence level 3 or 4; or evidence extrapolated from studies rated as 2 +
Good practice point	Recommended best practice based on the clinical experience of the guideline development group

Appendix 2 Example examination reports for basic and detailed first-trimester fetal ultrasound scans



Name of Center

Empty space for
logo of center

Basic examination 1st Trimester

Date: of exam

Patient ID:

Patient name:

Birth Date:

Sonographer:

Ultrasound machine:

Transabdominal ☐ Transvaginal ☐

Indication for scan:

Screening ☐ Other: _____

Relevant risk factors:

ART pregnancy: N/Y

Singleton: ☐

Twins**: ☐ monochorionic / dichorionic

Adnexa: Normal ☐ Abnormal ☐ Not examined ☐

Measurement	mm
Crown Rump Length (CRL)	
Biparietal Diameter (BPD)	
Nuchal Translucency (NT)	
Other	

Gestational Age based on Ultrasound:wd

Sonographic Appearance of Fetal Anatomy

Normal = N

Abnormal = A

Not visualized = NV

	N	A	NV
Head and Brain Head shape, ossification Falx present, butterfly-shape choroid plexus			
Heart Intrathoracic position Regular rhythm			
Abdomen Stomach present, abdominal wall intact Bladder not dilated			
Extremities Upper limbs with three segments Lower limbs with three segments			
Placenta Normal appearance without cystic structures			
Other			

CONCLUSION:

- ☐ Normal and complete examination.
☐ Normal but incomplete examination.
☐ Abnormal examination*
☐ Plans: ☐ No further ultrasound scans required
☐ Follow up planned in weeks.
☐ Referred to
☐ Other:

cfDNA test: planned ☐

Remarks:

(* Describe here any abnormal findings)

Signed:

** : For multiple pregnancy, specify chorionicity and fill out one sheet for each fetus (labeled Fetus A, B, C, . . .)



Name of Center

Empty space for
logo of center

Detailed examination 1st Trimester

Date: of exam

Patient name:

Patient ID:

Birth Date:

Sonographer:

Ultrasound machine:

Transabdominal



Transvaginal



Indication for scan:

Screening



Other:

Relevant risk factors:

ART pregnancy: N/Y

Singleton: ☐Twins**: ☐ monochorionic / dichorionicAdnexa: Normal ☐ Abnormal ☐ Not examined ☐Placenta: Normal ☐ Abnormal ☐

Biometry	mm
Crown Rump Length (CRL)	
Biparietal Diameter (BPD)	
Head Circumference (HC)	
Abdominal Circumference (AC)	
Femoral diaphysis length (FL)	

Risk assessment	
Nuchal Translucency (NT) (mm)	
Nasal Bone (NB) (mm)	
Ductus venosus A-Wave (positive/negative/PI)	
Tricuspid valve regurgitation N / Y	
Right Uterine Artery PI:	
Left Uterine Artery PI:	

Gestational Age based on Ultrasound:wd

CVS/Amnio: planned ☐cfDNA: planned ☐**CONCLUSION:**☐ Normal and complete examination.☐ Normal but incomplete examination.☐ Abnormal examination*☐ Plans: ☐ No further ultrasound scans required☐ Follow up planned in weeks.☐ Referred to☐ Other:

Remarks: (* Describe here any abnormal findings)

Sonographic Appearance of Fetal Anatomy		N	A	NV
Normal = N Abnormal = A Not visualized = NV				
Head and brain	Intact cranium / normal shape			
	Midline falx			
	Choroid plexus-Lateral ventricles			
	IT-Brainstem-cisterna magna			
	Cerebral peduncles with AoS			
Face - Neck	Nuchal translucency			
	Retronasal triangle			
	Maxilla-Mandible			
	Orbits			
Thorax	Thorax shape with lung fields			
	Diaphragmatic continuity			
Heart	Heart intrathoracic with regular rhythm			
	Cardiac size and axis			
	Four-chamber-view			
	Left ventricular outflow tract			
	Right ventricular outflow tract			
	Three-vessels and trachea view			
Abdomen	Stomach filled			
	Bladder filled (length <7mm)			
	Intact abdominal wall			
	Two umbilical arteries			
	Kidneys			
Spine				
Limbs	Upper limbs with three segments			
	Lower limbs with three segments			

Signed:

**: For multiple pregnancy, specify chorionicity and fill out one sheet for each fetus (labeled Fetus A, B, C, ...)

amnio, amniocentesis; AoS, xxxxxxxxxxxxxxxxxxxx; ART, assisted reproductive technology; cf DNA, cell-free DNA; CVS, chorionic villus sampling; d, days; N, no (except where defined as 'normal'); IT, intracranial translucency; PI, pulsatility index; w, weeks; Y, yes.

+A: SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figures S1 and S2 Full-size versions of Figures 1 and 2.