

# Quality Requirements for the early Fetal Ultrasound Assessment at 11–13<sup>+6</sup> Weeks of Gestation (DEGUM Levels II and III)

## Qualitätsanforderungen an die weiterführende differenzierte Ultraschalluntersuchung in der pränatalen Diagnostik (DEGUM-Stufen II und III) im Zeitraum 11–13<sup>+6</sup> Schwangerschaftswochen

### Authors

C. von Kaisenberg<sup>1</sup>, R. Chaoui<sup>2</sup>, M. Häusler<sup>3</sup>, K. O. Kagan<sup>4</sup>, P. Kozłowski<sup>5</sup>, E. Merz<sup>6</sup>, A. Rempen<sup>7</sup>, H. Steiner<sup>8</sup>, S. Tercanli<sup>9</sup>, J. Wisser<sup>10</sup>, K.-S. Heling<sup>2</sup>

### Affiliations

Affiliation addresses are listed at the end of the article.

### Key words

- nuchal translucency
- anatomy scanning
- fetal anomalies
- first trimester

received 9.2.2016  
accepted 8.3.2016

### Bibliography

DOI <http://dx.doi.org/10.1055/s-0042-105514>  
Published online: April 19, 2016  
Ultraschall in Med 2016; 37: 297–302 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0172-4614

### Correspondence

**Prof. Constantin von Kaisenberg**

Obstetrics and Gynecology,  
Hannover Medical School  
Carl-Neuberg-Str. 1  
30625 Hannover  
Germany  
Tel.: ++ /49/1 76/15 32 34 54  
Fax: ++ 49/5 11/5 32 61 45  
vonkaisenberg.constantin@mh-hannover.de

### Abstract

The early fetal ultrasound assessment at 11–13<sup>+6</sup> weeks of gestation remains the cornerstone of care despite the progress in diagnosing fetal chromosomal defects using cell-free fetal DNA (cffDNA) from the maternal circulation. The measurement of nuchal translucency (NT) allows the risk calculation for the fetal trisomies 21, 18 and 13 but also gives information on those fetal chromosomal defects which are at present unable to be detected using cffDNA. Nuchal translucency is the only auditable parameter at 11–13<sup>+6</sup> weeks and gives thus information on the quality of the first trimester anomaly scan. In addition it gives indirect information on the risks for fetal defects and for cardiac anomalies. Also the chances for a healthy live baby can be estimated. As experience with first trimester anomaly scanning increases, and the resolution of the ultrasound equipment has increased substantially, more and more details of the fetal anatomy become accessible at the first trimester scan. Therefore fetal anatomical defects and complex anomalies have become amenable to examination in the first trimester. This guideline describes compulsory and optional parameters for investigation at the first trimester scan and outlines a structured method of examining a first trimester fetus at 11–13<sup>+6</sup> weeks of gestation.

### Introduction

The present recommendation of the DEGUM Section Obstetrics and Gynecology for the quality requirements of the early fetal ultrasound assessment at 11–13<sup>+6</sup> weeks of gestation updates the version of 2004 [1]. It addresses specialized ultra-

### Zusammenfassung

Die frühe Ultraschalluntersuchung zwischen 11–13<sup>+6</sup> Schwangerschaftswochen stellt trotz der Fortschritte in der molekularen Diagnostik von Chromosomenstörungen aus dem Blut der Mutter (cffDNA) die Grundlage für Diagnostik und Therapie sowie des Schwangerschaftsmanagement dar. Die Messung der fetalen Nackentransparenz (NT) ermöglicht die Risikoberechnung für die fetalen Trisomien 21, 18 und 13 und liefert auch Informationen über solche fetalen Chromosomenstörungen, welche gegenwärtig durch cffDNA nicht erkannt werden können. Die fetale Nackentransparenzmessung ist der einzige audierbare Parameter zwischen 11–13<sup>+6</sup> SSW und gibt so Auskunft über die Qualität der Ersttrimester Fehlbildungsdiagnostik. Zusätzlich liefert sie indirekte Informationen über die Risiken für Fehlbildungen und Herzfehler. Auch kann die Wahrscheinlichkeit für die Geburt eines lebenden gesunden Babys abgeschätzt werden. Während die Erfahrung mit der Ersttrimester Fehlbildungsdiagnostik steigt und die Auflösung der Ultraschallgeräte substanziell zugenommen hat, werden mehr und mehr Details der fetalen Anatomie einer Untersuchung im ersten Trimenon zugänglich. Es werden obligatorische und fakultative Untersuchungsschritte für den Ersttrimester Fehlbildungsschall beschrieben und ein strukturierter Untersuchungsgang aufgezeigt, um einen Ersttrimesterfeteten zum Zeitpunkt 11–13<sup>+6</sup> Schwangerschaftswochen zu untersuchen.

sonographers (DEGUM Levels II & III). During the recent years there have been many changes which made an update of the previous version necessary. In particular the following aspects should be mentioned:

- ▶ Improvements in the resolution of ultrasound and increasing experience of operators allow a very detailed examination of the first trimester fetus if conditions are favourable. Therefore, beyond the measurement of the nuchal translucency, a detailed anatomical survey and early detection of major or complex anomalies can be achieved.
- ▶ With the introduction of the Gendiagnostikgesetz (GenDG) in 2009 and the Schwangerschaftskonfliktgesetz (SchKG) extensive counseling of the pregnant woman has become compulsory [2, 3]. Also the directive of the Gendiagnostik-Kommission of the Robert Koch Institute (GDKO directives of the RKI) on the requirements for the qualification of genetic counseling and the content and the requirements for the implementation of the antenatal risk assessment should be considered [4, 5]. In Austria the pregnant woman must be counseled by a specialist on the nature, consequences and significance of the suggested technique (genetische Analyse gem. §68 GTG (Gentechnikgesetz)) if NIPT is done [6]. In Switzerland there is an obligation for counselling about the significance and potential consequences of prenatal examinations for risk assessment [7].
- ▶ The introduction of non-invasive prenatal testing (NIPT) in 2012 based on the examination of the cell-free fetal DNA (cffDNA) in the maternal blood has as a further screening test yielded very high detection rates predominantly for trisomy 21, but also for the trisomies 18 and 13. First trimester ultrasound however can achieve much more than the risk calculation for chromosomal abnormalities only.
- ▶ Beyond fetal anomalies, using ultrasound among others, risk factors for the main problems of pregnancy can be established. This knowledge may lead to the early identification and therapy of high risk patients thus reducing the risks of the subsequent manifestation of the disease later in pregnancy and to be able to manage pregnancies individually according to their risks [8].

The DEGUM quality requirements for the ultrasound examination in early pregnancy (4–14 wks) are dealt with separately. There, dating of pregnancy based on ultrasound parameters is described in detail [9].

### Objectives of the ultrasound examination

There are a number of objectives for the examination in early pregnancy which may differ according to the problem in question, the history and risk factors. This is the first detailed ultrasound examination in pregnancy which allows an early assessment of the fetal anatomy. Thus at this early stage major fetal anomalies can be detected. Doubting and fear of the future parents can therefore be taken away in particular when there is a risk of recurrence for a specific anomaly. The present recommendation describes a structured examination at 11–13<sup>+6</sup> weeks' of gestation.

Many couples participate in first trimester screening mainly to get a result of the fetal risk for a chromosomal abnormality. If the risks are high or there is a suspicion of an anomaly an invasive procedure can be offered to make a diagnosis [9]. In case of a major anomaly the patient can be counseled in a multidisciplinary team and be supported in the decision making. If the decision is termination it can be done early in pregnancy. This may help in avoiding late terminations which have higher risks for the mother and are felt to be more stressful both for patients, relatives and medical personnel.

### Prerequisites & technical aspects

One of the prerequisites to carry out an anomaly scan at 11–13<sup>+6</sup> weeks of gestation is a profound knowledge in the ultrasound assessment of the fetus. Expertise can be demonstrated for example in obtaining the DEGUM levels II and III. Risk assessment for fetal chromosomal defects requires licencing through the Fetal Medicine Foundation (FMF) of Germany or the United Kingdom. In Germany first trimester screening is subject to the Gendiagnostikgesetz, therefore, prior to the scan, the woman must be counseled for the content of the examination and the potential consequences. It may be useful to let the women confirm the content of the discussion in written [2, 4, 5].

The scan can be performed transabdominally or vaginally. An advantage of the transabdominal scan is the better visualization of the whole content of the amniotic sac and measurements are easier to perform. An advantage of the vaginal approach is the better resolution but the route may be more time consuming. With a retroflexed uterus, bowel interponation, adipous abdominal walls or the suspicion of anomalies an additional vaginal scan may be helpful.

A variety of techniques may be included in first trimester screening such as B-mode, color doppler, pulsed wave doppler and 3D sonography. At this gestation, the fetus is at a critical period of its development. Therefore knowledge of the principles of risk reduction using dopplers is mandatory. In particular the use of pulsed spectral doppler sonography imposing the highest energetic strain should be particularly considered. Therefore the use of dopplers should both be subject to an indication and exposure reduced to a minimum (ALARA = as low as reasonably achievable) [11]. The heart rate can also be determined using pulsed wave dopplers on a free loop of the umbilical cord or can be measured using M-mode. Color doppler applied in early fetal echocardiography imposed no risks (◉ Table 1).

### Nuchal translucency & risk assessment for fetal chromosomal defects

Ultrasound will remain the most important technique in assessing the individual risks for aneuploidy despite the increasing use of cffDNA. The measurement of nuchal translucency (NT) is central as it gives information on chromosomal abnormalities which can not be detected using cffDNA, genetic syndromes and fetal structural defects [12–16]. Also the chances for intrauterine fetal death and for a healthy live birth can be assessed [17]. The use of cffDNA should only be offered once the woman has been counseled about the nature, consequences and significance of the test [18, 19]. As the accuracy of the fetal NT measurement and risk calculation is depending on the quality of the examination, the measurement must be done adhering to the guidelines of the Fetal Medicine Foundation and is subject to annual audit [20] (◉ Table 2, ◉ Fig. 1).

Risk assessment for fetal trisomy 21 should be done through combined first trimester screening (combined test). In addition to the NT, free beta-hCG and PAPP-A must be measured [13, 14, 20–22]. These parameters should be evaluated simultaneously, not sequentially, together with maternal age and gestational age through the programs of the FMF. Only the background risk and the adjusted risk should be communicated respectively. The detection rate for the combined first trimester screening is about 90% for a false-positive rate of 3–5% [21, 23–25]. If the blood

**Table 1** Technical requirements for ultrasound machines.

– real-time, grey-scale, two-dimensional image (2D), B-mode
– abdominal probes (electronic and/or mechanical curved-array or linear probes), broadband (frequency range 3.0 – 7.5 MHz) and / or transvaginal electronic or mechanical probes, broadband, high frequency (4.0 – 10.0 MHz)
– freeze and online-zoom capability
– video-cine-loop capability
– electronic caliper, minimal discrimination 0.1 mm
– storage and print facilities for images
– regular technical audit (see also Ultraschallvereinbarung)

for biochemistry is being taken a week or two earlier detection rates may even be higher.

In dichorionic twins the risk for each fetus is calculated individually. As monochorionic (MC) twins are always monozygotic only one risk for counseling should be used. This can be derived from the mean of the two risks calculated individually for each fetus. The presence of a big difference in the NT of MC twins may suggest the subsequent development of a twin-to-twin transfusion syndrome [26].

The detection rate may further be increased through the inclusion of the fetal nasal bone, the ductus venosus or tricuspid valve flow [27 – 30]. If these additional parameters are to be included in the risk calculation further certification through the FMF is required [27 – 30]. If detection rates are to be increased both cffDNA analysis and/or the assessment of additional ultrasound parameters have to be considered [18].

### Fetal anomaly scanning at 11 – 13<sup>+6</sup> weeks of gestation

Standard measurements at 11 – 13<sup>+6</sup> weeks of gestation are the crown-rump-length (CRL), the biparietal diameter (BPD) and nuchal translucency (NT). The head circumference may be used for dating from 14 weeks. Further measurements are optional (Table 3).

A detailed anatomical survey is done best in the second trimester [31, 32], but many anatomical structures can already be identified in the first [33]. The visualisation of details is depending on a variety of factors such as the fetal size (45 – 84 mm), the route (transvaginal vs transabdominal), the maternal habitus, the resolution of the ultrasound machine and the training of the operator. In many cases a reliable assessment can be achieved today using the transabdominal route. The following structures can usually be assessed (Table 4).

#### Head and Brain

The head and brain can be simultaneously assessed when the BPD is taken [33, 34]. In a transverse section the ovoid shape of the fetal head, the intact bone of the skull and the falx cerebri separating both hemispheres can be demonstrated. Both choroid plexus are prominent in early gestation filling almost completely the lateral ventricles sometimes slightly asymmetrical [34, 45]. A median sagittal section of the fetal head is the basis for the measurement of the NT. But additional structures of the fetal brain in the posterior fossa should also be considered, such as the fourth ventricle or intracranial translucency (IT) and the brain stem as they may be helpful in early detection of open spina bifida [36, 37] (Fig. 1).

**Table 2** FMF-Protocol for the measurement of the fetal nuchal translucency (NT) (Fig. 1).

– 11 <sup>+0</sup> – 13 <sup>+6</sup> weeks of gestation
– crown-rump-length 45 – 84 mm
– magnification: fetal head and thorax occupy the whole screen
– mid-sagittal view: tip of the nose and rectangular shape of the palate anteriorly, the translucent diencephalon in the centre and the nuchal membrane posteriorly <sup>1</sup>
– neutral position
– distinguish between the fetal skin and amnion
– measure widest area of NT
– placing the calipers: 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
– turn caliper down when magnifying the image
– make more than one image, record maximum one in database which meets all of the above criteria
– semi-automated technique may be used
– nuchal cord: use mean of NT from above and below the cord

<sup>1</sup> 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.



**Fig. 1** Fetus at 12<sup>+6</sup> weeks of gestation with normal nuchal translucency. Note the nasal bone (NB), the Thalamus (T), the Midbrain (M), the Brain Stem (BS), the Intracranial Translucency (IT), the Cisterna magna (CM), the Nuchal Translucency (NT) and the Amnion.

#### Face

The face is best viewed in a median sagittal plane (profile) and in frontal and/or transversal views demonstrating the eyes and maxilla and mandible.

#### Neck and Spine

The standard view to measure NT is a dorsoanterior or dorsoanterior median sagittal plane of the fetus (Fig. 1). If the nuchal is increased additional transversal views may be helpful to assess more details. An increased NT is associated with fetal anomalies [38].

**Table 3** Ultrasound first trimester standard biometry and optional parameters.

standard biometry	optional parameters
crown-rump-length (CRL)	
biparietal diameter (BPD)	head- and -abdominal circumference (HC, AC), femur length (FL)
nuchal translucency (NT) <sup>1</sup>	nasal bone (NB) <sup>1</sup>
	intracranial translucency (IT) / brain stem
	fetal heart rate (FHR)
	trikuspid flow (TR) <sup>1</sup>
	ductus venosus flow (DV) <sup>1</sup>
	uterine arteries (UA) <sup>1</sup>
	cervical length (Cx) <sup>1</sup>

<sup>1</sup> After counselling and consenting (GenDG) and certification through the FMF: NT, NB, TR, DV, UA, Cx.

**Table 4** Ultrasound standard views of the fetal anatomy and optional parameters [42 – 45].

	standard views	optional parameters
skull / brain	bone of the skull, falx cerebri, choroid plexus	intracranial translucency IT brain stem
face	profile	eyes, maxillary and mandible, lips
neck	nuchal translucency (NT) <sup>1</sup>	nasal bone (NB) <sup>1</sup>
spine		outline
heart / thorax	position, contour four chamber view lungs	outflow tracts (color) three-vessel-trachea view tricuspid flow (TR) <sup>1</sup>
abdomen	stomach abdominal wall	diaphragm ductus venosus flow (DV) <sup>1</sup> umbilical arteries and urinary bladder
extremities	arms & legs	hands & feet (femur tibia fibula humerus radius ulna)
urogenital tract	urinary bladder	kidneys
plazenta	chorionicity, amnionicity (multiple gestation), structure	position, insertion of umbilical cord uterine arteries <sup>1</sup>

<sup>1</sup> After counselling and consenting (GenDG) and certification through the FMF: NT, NB, TR, DV, UA, Cx.

The spine can be best viewed in sagittal and transversal planes but many anomalies may remain undetected at 11 – 13<sup>6</sup> weeks.

### Heart and Thorax

The heart, lungs and thorax can best be viewed at the level of the four chamber view. The heart rate may be taken. A B-mode may be used to assess the heart, but color doppler facilitates the investigation and increases the accuracy. The four chamber view and the three vessel trachea view should be demonstrated thus enabling the detection of a number of anomalies.

The measurement of the NT, of the flow across the tricuspid valve and in the Ductus venosus is an indirect method of screening for cardiac defects [39].

### Abdomen

Sagittal and transversal views are among important planes to assess the anterior abdominal wall and internal abdominal organs. The following landmarks should be looked at: stomach, urinary bladder and intact abdominal wall. Using color doppler the umbilical arteries around the urinary bladder can be visualized [40]. A clear depiction of the kidneys is not always possible at this gestation. A physiological omphalocele may be noted from 9 and 11 weeks.

### Extremities

The extremities can usually be clearly demonstrated. The presence of three segments on each extremity should be looked at. In selected cases such as with an increased recurrence risk it may be important to look at individual fingers and toes which may be easier transvaginally.

### Placenta and amniotic fluid

The site and morphology of the placenta should be looked at. In multiple gestation pregnancies chorionicity and amnionicity should be documented. The diagnosis of placenta praevia or an abnormal placentation should be made at a later stage of pregnancy. The insertion of the cord at the placenta is often feasible. Amniotic fluid is usually normal in early pregnancy.

### Limitations in assessing fetal anatomy at the first trimester scan

In experienced hands a number of major anomalies can be detected through a systematic scan. However there are limitations to the method as the anatomy is at an early stage of development [41]. The patient should be informed about the limitations and 2<sup>nd</sup> trimester screening for anomalies should be recommended [32].

### Management of abnormal or suspicious findings

The findings of an abnormality or an increased risk of a chromosomal defect should prompt an invasive procedure. Chorionic villos sampling (CVS) is the standard technique as it gives results within a day. In that case, cffDNA analysis is not indicated as only a limited spectrum of aneuploidies can be detected and the test has no diagnostic reliability.

In the case of an intermediate risk further assessment involving additional ultrasound markers such as the nasal bone and tricuspid and ductal flows can be carried out. In that group more detailed ultrasound assessment may be replaced by a cffDNA test. In fetuses with abnormal anatomy but normal karyotype using conventional cytogenetics, parents should be counselled about the possibility of CGH-Array-Analysis. If the NT is >95. centile the association with genetic syndromes and structural anomalies such as a cardiac defect should be considered. In those cases anomaly scanning at 16 and 20 weeks including fetal echocardiography may be useful. Genetic counselling may help identifying familiar single gene disorders which may be amenable for sequencing in the present pregnancy.

In the case of low free beta hCG and PAPP-A (<0.41 MoM) serial follow-up scans to monitor for intrauterine growth restriction (IUGR), pre-eclampsia (PET) and for imminent intrauterine fetal death [46] is advisable.

The significance of early diagnosed fetal anomalies is in some cases difficult to predict as there may be spontaneous resolution or worsening of the condition. The prognosis may become more



clear at serial scans. A second opinion and an interdisciplinary approach should be encouraged.

## Future prospects

Ultrasound is the basis of first trimester screening at 11–13<sup>+6</sup> weeks of gestation including the structural and hemodynamical examination of the fetus and mother in combination with assessment of the background risks and biochemical and biophysical factors [7].

Research focuses at present on the development and advancement of risk algorithms for chromosomal abnormalities, for intrauterine fetal death / stillbirth, intrauterine growth restriction and pre-eclampsia, for preterm birth and for macrosomia and diabetes mellitus [47–52] and on the integration of rapidly evolving molecular techniques.

For the risk assessment algorithms may be used which can publicly be accessed or are subject of certification (<https://fetalmedicine.org/pyramid-of-care>).

For individual diseases there is already an early intervention, a potential reduction of maternal and fetal morbidity and mortality is currently under intensive investigation.

## Affiliations

- <sup>1</sup> Obstetrics and Gynecology, Hannover Medical School, Hannover, Germany
- <sup>2</sup> Praxis für Pränatalmedizin, Berlin, Germany
- <sup>3</sup> Obstetrics and Gynecology, University of Graz, Graz, Austria
- <sup>4</sup> Obstetrics and Gynecology, University of Tübingen, Germany
- <sup>5</sup> Praenatal-Medizin und Genetik, Düsseldorf, Germany
- <sup>6</sup> Obstetrics and Gynecology, Krankenhaus Nordwest, Frankfurt/Main, Germany
- <sup>7</sup> Frauenklinik, Evangelisches Diakoniekrankenhaus, Schwäbisch-Hall, Germany
- <sup>8</sup> Ordination Salzburg, Salzburg, Austria
- <sup>9</sup> Pränatalmedizin, Ultraschallpraxis Freie Straße, Basel, Switzerland
- <sup>10</sup> Obstetrics and Gynecology, University of Zurich, Zurich, Switzerland

## References

- 1 DEGUM III Guideline For Level II Ultrasound Examinations at 11–14 Weeks of Gestation. *Ultraschall in Med* 2004; 25: 218–220
- 2 Bundesministerium der Justiz und für Verbraucherschutz. Gesetz über genetische Untersuchungen bei Menschen (Gendiagnostikgesetz – GenDG). *Bundesgesetzblatt [Internet]* 2009 Jul 31
- 3 Bundesministerium der Justiz und für Verbraucherschutz. Gesetz zur Vermeidung und Bewältigung von Schwangerschaftskonflikten (Schwangerschaftskonfliktgesetz – SchKG). *Bundesgesetzblatt* 1992 Jul 27
- 4 Richtlinie der Gendiagnostik-Kommission (GEKO) für die Anforderungen an die Durchführung der vorgeburtlichen Risikoabklärung sowie an die insoweit erforderlichen Maßnahmen zur Qualitätssicherung gemäß 23 Abs. 2 Nr. 5 GenDG. *Bundesgesundheitsbl* 2013; 56: 1023–1027
- 5 Richtlinie der Gendiagnostik-Kommission (GEKO) über die Anforderungen an die Qualifikation zur und Inhalte der genetischen Beratung gemäß 23 Abs. 2 Nr. 2a und 23 Abs. 2 Nr. 3 GenDG. *Bundesgesundheitsbl* 2011; 54: 1248–1256
- 6 Gentechnikgesetz – GTG und Änderung des Produkthaftungsgesetzes Österreich 510. *Bundesgesetzblatt* 1994, Jul 12
- 7 Bundesgesetz über genetische Untersuchungen beim Menschen (GUMG) vom 8. Oktober 2004 (Stand am 1. Januar 2014) Die Bundesversammlung der Schweizerischen Eidgenossenschaft, AS 2007 635, published online. <http://www.admin.ch/opc/de/classified-compilation/20011087/index.html>
- 8 Nicolaidis KH. A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment. *Prenat Diagn* 2011; 31: 3–6
- 9 Rempen A. Standards in ultrasound examination in early pregnancy. Recommendation of DEGUM Stage III of the German Society of Ultra-

- sound in Medicine (Gynecology and Obstetrics Section) and ARGUS (Working Group of Ultrasound Diagnosis of DGGG). *Z Geburtshilfe Neonatol.* 2001; 205: 162–165
- 10 Kähler C, Gembruch U, Heling KS et al. Empfehlungen der DEGUM zur Durchführung von Amniozentese und Chorionzottenbiopsie. *Ultraschall in Med* 2013; 34: 435–440
  - 11 Salvesen KÅ, Lees C, Abramowicz J et al. Safe use of Doppler ultrasound during the 11 to 13 + 6-week scan: is it possible? *Ultrasound Obstet Gynecol* 2011; 37: 625–628
  - 12 Kagan KO, Hoopmann M, Hammer R et al. Screening for chromosomal abnormalities by first trimester combined screening and noninvasive prenatal testing. *Ultraschall in Med* 2015; 36: 40–46
  - 13 Gasiorek-Wiens A, Tercanli S, Kozlowski P. German-Speaking Down Syndrome Screening Group. et al. Screening for trisomy 21 by fetal nuchal translucency and maternal age: a multicenter project in Germany, Austria and Switzerland. *Ultrasound Obstet Gynecol* 2001; 18: 645–648
  - 14 von Kaisenberg CS, Gasiorek-Wiens A, Bielicki M et al. Screening for trisomy 21 by maternal age, fetal nuchal translucency and maternal serum biochemistry at 11–14 weeks: a German multicenter study. *J Matern Fetal Neonatal Med* 2002; 12: 89–94
  - 15 Souka AP, von Kaisenberg CS, Hyett JA et al. Increased nuchal translucency with normal karyotype. *American Journal of Obstetrics and Gynecology* 2005; 192: 1005–1021
  - 16 Hyett JA, Perdu M, Sharland GK et al. Increased nuchal translucency at 10–14 weeks of gestation as a marker for major cardiac defects. *Ultrasound Obstet Gynecol* 1997; 10: 242–246
  - 17 Nicolaidis KH, von Kaisenberg CS. Die Ultraschalluntersuchung von 11–13+6 Schwangerschaftswochen. London 2004: p 78
  - 18 Kagan KO, Schmid M, Hoopmann M et al. Screening Performance and Costs of Different Strategies in Prenatal Screening for Trisomy 21. *Geburtsh Frauenheilk* 2015; 75: 244–250
  - 19 Schmidt M, Klaritsch P, Arzt W et al. Drei Länder – Empfehlung zum Einsatz von Nicht-invasiven pränatalen Tests (NIPT) zur Analyse der zellfreien DNA (cfDNA) im mütterlichen Blut zum Screening auf fetale Chromosomenstörungen in der klinischen Praxis. *Ultraschall in Med* 2015; 36: 507–510
  - 20 Kagan KO, Wright D, Etchegaray A et al. Effect of deviation of nuchal translucency measurements on the performance of screening for trisomy 21. *Ultrasound Obstet Gynecol* 2009; 33: 657–664
  - 21 Merz E, Thode C, Eiben B et al. Individualized correction for maternal weight in calculating the risk of chromosomal abnormalities with first-trimester screening data. *Ultraschall in Med* 2011; 32: 33–39
  - 22 Kagan KO, Wright D, Spencer K et al. 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
  - 23 Kagan KO, Wright D, Valencia C et al. Screening for trisomies 21, 18 and 13 by maternal age, fetal nuchal translucency, fetal heart rate, free beta-hCG and pregnancy-associated plasma protein-A. *Hum Reprod* 2008; 23: 1968–1975
  - 24 Kagan KO, Etchegaray A, Zhou Y et al. Prospective validation of first-trimester combined screening for trisomy 21. *Ultrasound Obstet Gynecol* 2009; 34: 14–18
  - 25 Merz E, Thode Ch, Eiben B et al. Prenatal risk calculation PRC 3.0: an extended DOE-based first-trimester screening algorithm allowing for early blood sampling. *US Med* 2015; in press
  - 26 Kagan KO, Gazzoni A, Sepulveda-Gonzales G et al. Discordance in nuchal translucency thickness in the prediction of severe twin-to-twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2007; 29: 527–532 Published online. DOI: 10.1002/uog.4006
  - 27 Kagan KO, Cicero S, Staboulidou I et al. 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
  - 28 Kagan KO, Valencia C, Livanos P et al. 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
  - 29 Maiz N, Nicolaidis KH. Ductus venosus in the first trimester: contribution to screening of chromosomal, cardiac defects and monochorionic twin complications. *Fetal Diagn Ther* 2010; 28: 65–71
  - 30 Maiz N, Valencia C, Kagan KO et al. 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

- 31 Salomon LJ, Alfievic Z, Berghella V et al. ISUOG Practice guidelines for performance of the routine mid-trimester fetal ultrasound scan. *Ultrasound in Obstetrics and Gynecology* 2011; pp 116–126
- 32 Merz E, Eichhorn KH, von Kaisenberg C et al. Aktualisierte Qualitätsanforderungen an die weiterführende differenzierte Ultraschalluntersuchung in der pränatalen Diagnostik (= DEGUM-Stufe II) im Zeitraum von 18+0 bis 21+6 Schwangerschaftswochen. *Ultraschall in Med* 2012; 33: 593–596
- 33 von Kaisenberg CS, Kühling-von Kaisenberg H, Fritzer E et al. Fetal transabdominal anatomy scanning using standard views at 11 to 14 weeks' gestation. *American Journal of Obstetrics and Gynecology* 2005; 192: 535–542
- 34 von Kaisenberg CS, Fritzer E, Kühling H et al. Fetal transabdominal biometry at 11–14 weeks of gestation. *Ultrasound Obstet Gynecol* 2002; 20: 564–574
- 35 Abu-Rustum RS, Ziade MF, Abu-Rustum SE. Reference values for the right and left fetal choroid plexus at 11 to 13 weeks: an early sign of “developmental” laterality? *J Ultrasound Med* 2013; 32: 1623–1629
- 36 Chaoui R, Benoit B, Mitkowska-Wozniak H et al. Assessment of intracranial translucency (IT) in the detection of spina bifida at the 11–13-week scan. *Ultrasound Obstet Gynecol* 2009; 34: 249–252
- 37 Lachmann R, Chaoui R, Moratalla J et al. Posterior brain in fetuses with open spina bifida at 11 to 13 weeks. Chitty LS, Lau TK, editors. *Prenat Diagn* 2011; 31: 103–106
- 38 Becker R, Wegner RD. Detailed screening for fetal anomalies and cardiac defects at the 11–13-week scan. *Ultrasound Obstet Gynecol* 2006; 27: 613–618
- 39 Khalil A, Nicolaides KH. Fetal heart defects: Potential and pitfalls of first-trimester detection. *Seminars in Fetal and Neonatal Medicine*. Elsevier Ltd 2013; 18: 251–260
- 40 Salomon LJ, Alfievic Z, Bilardo CM et al. ISUOG Practice Guidelines: performance of first-trimester fetal ultrasound scan. *Ultrasound Obstet Gynecol* 2012; 41: 102–113
- 41 Van Mieghem T, Hindryckx A, Van Calsteren K. Early fetal anatomy screening. *Current Opinion in Obstetrics and Gynecology* 2015; 27: 143–150
- 42 Fong KW, Toi A, Salem S et al. Detection of fetal structural abnormalities with US during early pregnancy. *Radiographics* 2004; 24: 157–174
- 43 McAuliffe FM, Fong KW, Toi A et al. Ultrasound detection of fetal anomalies in conjunction with first-trimester nuchal translucency screening: a feasibility study. *YMOB* 2005; 193: 1260–1265
- 44 Taipale P, Ammälä M, Salonen R et al. Learning Curve in Ultrasonographic Screening for Selected Fetal Structural Anomalies in Early Pregnancy. *Obstetrics & Gynecology* 2003; 101: 273–278
- 45 Khalil A, Papageorghiou A, Bhide A et al. Biparietal diameter at 11 to 13 weeks' gestation in fetuses with holoprosencephaly. *Prenat Diagn* 2014; 34: 134–138
- 46 Spencer K, Cowans NJ, Avgidou K et al. First-trimester ultrasound and biochemical markers of aneuploidy and the prediction of impending fetal death. *Ultrasound Obstet Gynecol* 2006; 28: 637–643
- 47 Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. *Prenat Diagn* 2011; 31: 7–15
- 48 Akolekar R, Bower S, Flack N et al. Prediction of miscarriage and stillbirth at 11–13 weeks and the contribution of chorionic villus sampling. Chitty LS, Lau TK, editors. *Prenat Diagn* 2011; 31: 38–45
- 49 Karagiannis G, Akolekar R, Sarquis R et al. Prediction of Small-for-Gestation Neonates from Biophysical and Biochemical Markers at 11–13 Weeks. *Fetal Diagn Ther* 2011; 29: 148–154
- 50 Akolekar R, Syngelaki A, Sarquis R et al. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11–13 weeks. *Prenat Diagn* 2011; 31: 66–74
- 51 Poon LCY, Karagiannis G, Stratieva V et al. First-Trimester Prediction of Macrosomia. *Fetal Diagn Ther* 2011; 29: 139–147
- 52 Nanda S, Savvidou M, Syngelaki A et al. Prediction of gestational diabetes mellitus by maternal factors and biomarkers at 11 to 13 weeks. *Prenat Diagn* 2010; 31: 135–141