Firsttrimester Diagnosis and Therapy @ 11 – 13+6 Weeks of Gestation – Part 2

Guideline of the DEGUM, ÖGUM, SGUMGG, DGGG, ÖGG, Gynecologie Suisse, DGPM, DGPGM, BVF, ACHSE (AWMF S2e LL 085-002 1.1.2024) (https://register.awmf.org/de/leitlinien/detail/085-002)

Ersttrimester Diagnostik und Therapie @ 11 – 13+6 Schwangerschaftswochen – Teil 2

Leitlinie der DEGUM, ÖGUM, SGUMGG, DGGG, ÖGG, Gynecologie Suisse, DGPM, DGPGM, BVF, ACHSE (AWMF S2e LL 085-002 1.1.2024) (https://register.awmf.org/de/leitlinien/detail/085-002)

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ABSTRACT

This extensive AWMF 085-002 S2e-guideline "First Trimester Diagnosis and Therapy @ 11 – 13+6 Weeks of Gestation" has systematically analyzed high-quality studies and publications and the existing evidence (evidence tables) and produced recommendations (level of recommendation, level of evidence, strength of consensus).

This guideline deals with the following topics in the context of the 11 – 13+6 weeks scan: the legal basis, screening for anatomical malformations, screening for chromosomal defects, quality assessment and audit, screening for preeclampsia and FGR, screening for preterm birth, screening for abnormally invasive placenta (AIP) and placenta accreta spectrum (PAS), screening for velamentous cord insertion and vasa praevia, screening for diabetes mellitus and LGA.

Screening for complications of pregnancy can best be carried out @ 11 – 13+6 weeks of gestation. The issues of how to identify malformations, chromosomal abnormalities and certain

disorders of placentation (high blood pressure and proteinuria, intrauterine growth retardation) have been solved. The problem of how to identify placenta percreta and vasa previa has been partially solved. What is still unsolved is how to identify disorders of glucose metabolism and preterm birth.

In the first trimester, solutions to some of these problems are available: parents can be given extensive counselling and the risk that a pregnancy complication will manifest at a later stage can be delayed and reduced. This means that screening is critically important as it helps in decision-making about the best way to manage pregnancy complications (prevention and intervals between follow-up examinations).

If no treatment is available and if a termination of pregnancy is considered, the intervention can be carried out with far lower complications compared to the second trimester of pregnancy. In most cases, further examinations are not required and the parents can be reassured. A repeat examination at around week 20 of gestation to complete the screening for malformations is recommended.

Note: The guideline will be published simultaneously in the official journals of both professional societies (i.e. Ultraschall in der Medizin/European Journal of Ultrasound for the DEGUM and Geburtshilfe und Frauenheilkunde for the DGGG).

ZUSAMMENFASSUNG

In dieser umfassenden AWMF 085-002 S2e-Leitlinie „Ersttrimester Diagnostik und Therapie @ 11–13^{+6} Schwangerschaftswochen“ werden die qualitativ hochwertigen Studien und Publikationen bzw. die vorliegende Evidenz (Evidence Tables) systematisch analysiert und Empfehlungen formuliert (Empfehlungsgrad, Evidenzgrad, Konsensstärke).

Die LL behandelt zum Zeitpunkt 11–13^{+6} Schwangerschaftswochen folgende Themen: rechtliche Grundlagen, Screening für Fehlbildungen, Screening für Chromosomenstörungen, Qualitätssicherung und Audit, Screening für Präeklampsie und FGR, Screening für Frühgeburt, Screening für Abnormal Invasive Placenta (AIP) und Placenta Accreta Spectrum (PAS), Screening für Insertio velamentosa und Vasa praevia, Screening für Diabetes mellitus und LGA. Der Zeitpunkt 11–13^{+6} Schwangerschaftswochen ermöglicht die Suche nach Schwangerschaftsproblemen. Gelöst ist die Suche nach Fehlbildungen, Chromosomenstörungen und Plazentaproblemen (hoher Blutdruck und Eiweißausscheidung, intrauterine Wachstumsretardierung). Zum Teil gelöst ist die Suche nach Placenta percreta und Vasa praevia. Ungelöst ist die Suche nach Glukosestoffwechselstörungen und Frühgeburt.

Für einen Teil der Probleme existieren im ersten Trimenon Lösungsansätze, die Eltern können intensiv beraten werden; die Wahrscheinlichkeit, dass sich ein Schwangerschaftsproblem später manifestiert, kann hinausgezögert und gesenkt werden. Dies macht die Untersuchung für die Entscheidungsfindung bezüglich des besten Managements (Intervalle der Follow-up-Untersuchungen und Prävention) unverzichtbar. Besteht keine Therapie bzw. wird ein Schwangerschaftsabbruch erwogen, kann dieser mit viel niedrigeren Komplikationsraten als im zweiten Trimenon angeboten werden. In den meisten Fällen sind weiterführende Untersuchungen nicht erforderlich und die Eltern können beruhigt werden. Eine erneute Untersuchung um 20 Schwangerschaftswochen zur Vervollständigung der Fehlbildungsdiagnostik wird empfohlen.

Hinweis: Die Leitlinie wird gleichzeitig in den offiziellen Zeitschriften beider Fachgesellschaften (d.h. Ultraschall in der Medizin/European Journal of Ultrasound für die DEGUM und Geburtshilfe und Frauenheilkunde für die DGGG) veröffentlicht.

5 Screening for Chromosomal Disorders @ 11–13^{+6} Weeks of Gestation

5.1 Statistical indicators to evaluate the quality of screening examinations

Four-field table (▶ **Table 1**)

▶ **Table 1** Four-field table.

Test result	Affected	Not affected	Total
Positive	(a)	(b)	a+b
Negative	(c)	(d)	c+d
Total	a+c	b+d	a+b+c+d

Sensitivity = a/(a+c)
Specificity = d/(b+d)
Positive predictive value = a/(a+b)
Negative predictive value = d/(c+d).

5.2 Frequency of chromosomal disorders

5.3 Counselling prior to screening

5.4 First-trimester screening

Basic approach for risk calculation

The risk calculation *must* only be carried out when all risk markers (maternal age, nuchal translucency, biochemistry serum tests) have been included.

The result should only be communicated after all risk markers have been taken into account.

Accordingly, only a risk before the test and after completion of the calculation must be communicated, **no intermediary steps should be taken**.

(Level of recommendation A, level of evidence 1a, strong consensus 12/12)

5.5 Risk algorithms

Age-related risk, gestational age and recurrence risk

Ultrasound-based screening methods

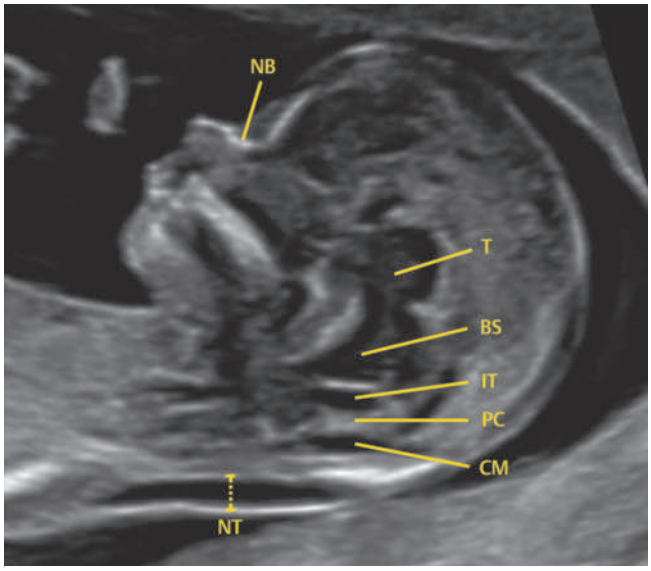
Fetal nuchal translucency

Methods and rules of measurement

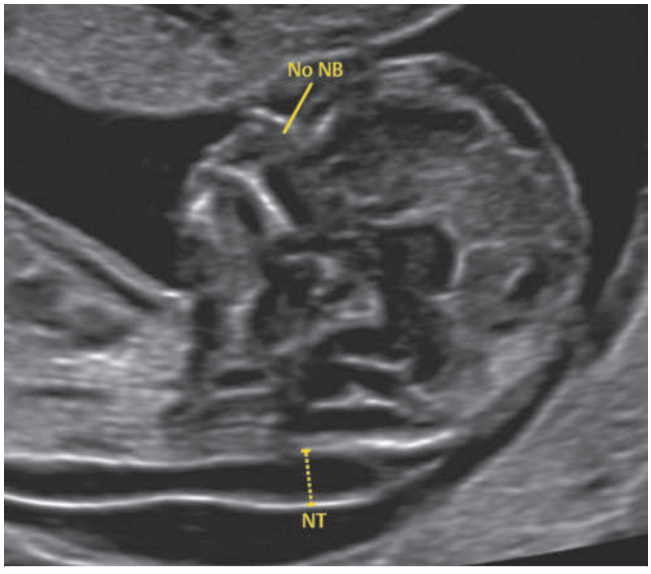
Protocol for measurement for **nuchal translucency** (FMF London)

- The gestational period must be 11 to 13 weeks and six days.
- The fetal crown-rump length should be between 45 and 84 mm.
- The magnification of the image should be such that the fetal head and thorax occupy the whole screen.
- A mid-sagittal view of the face should be obtained. This is defined by the presence of the echogenic tip of the nose and rectangular shape of the palate anteriorly, the translucent diencephalon in the centre and the nuchal membrane posteriorly. Minor deviations from the exact midline plane would cause non-visualization of the tip of the nose and visibility of the maxilla.
- The fetus should be in a neutral position, with the head in line with the spine. When the fetal neck is hyperextended the measurement can be falsely increased and when the neck is flexed, the measurement can be falsely decreased.
- Care must be taken to distinguish between fetal skin and amnion.
- The widest part of translucency must always be measured.
- Measurements should be taken with the inner border of the horizontal line of the callipers placed ON the line that defines the nuchal translucency thickness – the crossbar of the calliper should be such that it is hardly visible as it merges with the white line of the border, not in the nuchal fluid.
- In magnifying the image (pre or post freeze zoom) it is important to turn the gain down. This avoids the mistake of placing the calliper on the fuzzy edge of the line which causes an underestimate of the nuchal measurement.
- During the scan more than one measurement must be taken and the maximum one that meets all the above criteria should be recorded in the database.
- The umbilical cord may be round the fetal neck in about 5% of cases and this finding may produce a falsely increased NT.In such cases, the measurements of NT above and below the cord are different and, in the calculation of risk, it is more appropriate to use the average of the two measurements.

(Level of recommendation A, level of evidence 1b, strong consensus 12/12) (▶ **Figs. 1** and **2**, **Table 2**)



▶ **Fig. 1** Sagittal view of a fetus with normal nuchal translucency (NT), cisterna magna (CM), plexus choroideus (PC), intracranial translucency (IT), brainstem (BS), thalamus (T) and nasal bone (NB) @ 12^{+5} weeks of gestation. [rerif]

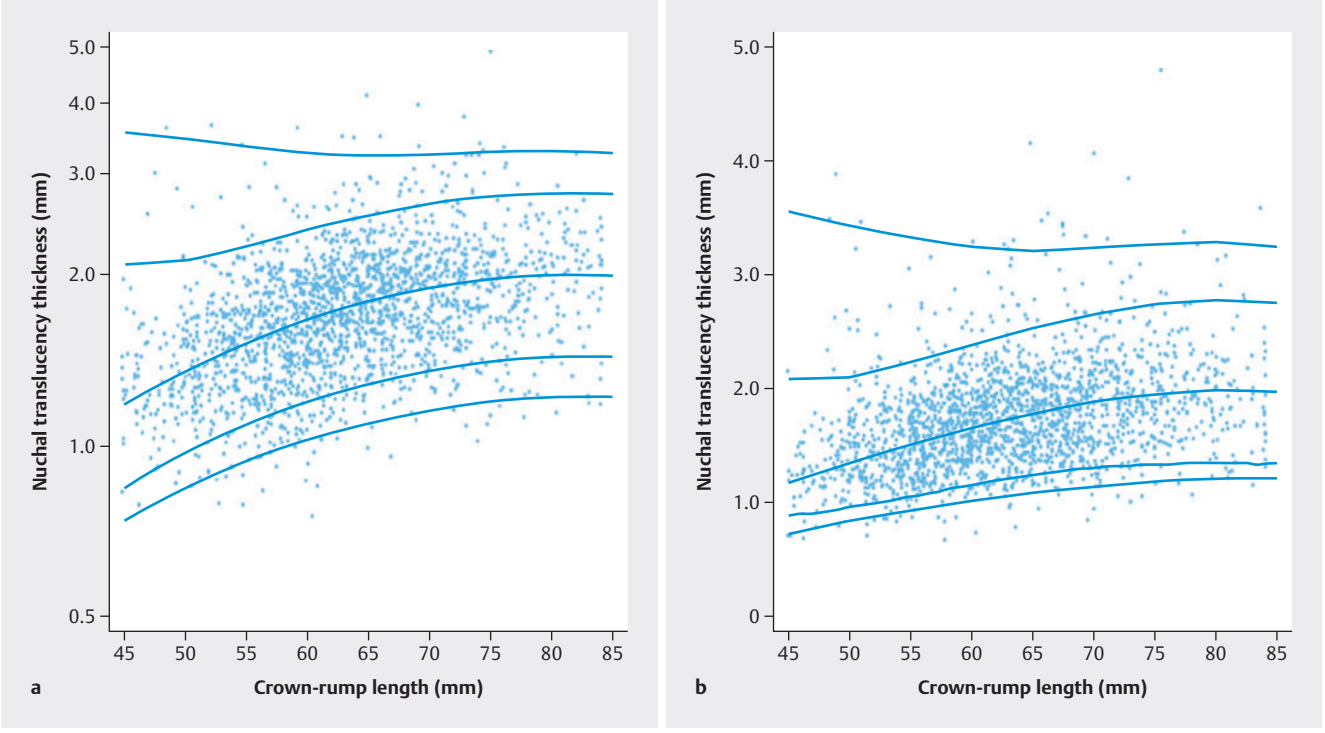


▶ **Fig. 2** Sagittal view of a trisomy 21 fetus with increased nuchal translucency (NT) and absent nasal bone (NB). [rerif]

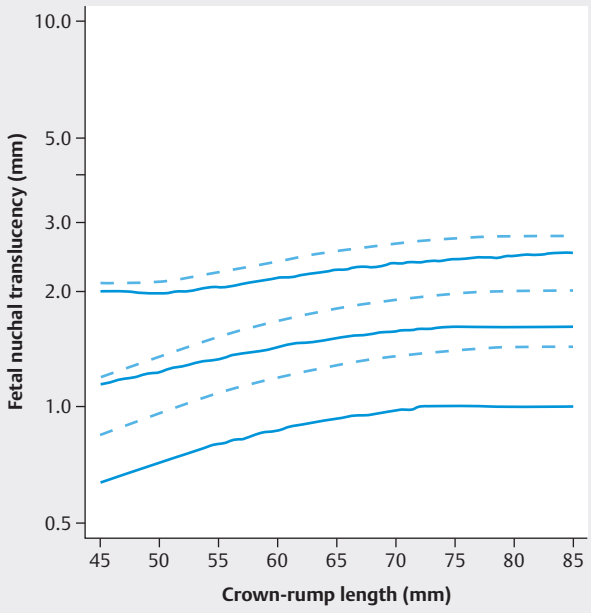
▶ **Table 2** Frequency of chromosomal disorders in second-trimester pregnancies based on maternal age at term [103].

	Trisomy 21	Trisomy 18	Trisomy 13	Sex chromosome aneuploidies (XXX, XY, XYY, 45,X)	Microarray or rare chromosomal disorders	All chromosomal disorders
Age 20	8 per 10 000 1 in 1250	2 per 10 000 1 in 5000	1 per 10 000 1 in 10 000	34 per 10 000 1 in 294	37 per 10 000 1 in 270	82 per 10 000 1 in 122
Age 25	10 per 10 000 1 in 1000	2 per 10 000 1 in 5000	1 per 10 000 1 in 10 000	34 per 10 000 1 in 294	37 per 10 000 1 in 270	84 per 10 000 1 in 119
Age 30	14 per 10 000 1 in 714	4 per 10 000 1 in 2500	2 per 10 000 1 in 5000	34 per 10 000 1 in 294	37 per 10 000 1 in 270	91 per 10 000 1 in 110
Age 35	34 per 10 000 1 in 294	9 per 10 000 1 in 1111	4 per 10 000 1 in 2500	35 per 10 000 1 in 285	37 per 10 000 1 in 270	119 per 10 000 1 in 84
Age 40	116 per 10 000 1 in 86	30 per 10 000 1 in 333	14 per 10 000 1 in 714	51 per 10 000 1 in 196	37 per 10 000 1 in 270	248 per 10 000 1 in 40

Distribution of nuchal translucency, reference ranges (▶ Figs. 3 and 4)



▶ **Fig. 3** Distribution of the nuchal translucency (FMF UK) depending on the crown-rump length in non-affected pregnancies. The median, 1st, 5th, 50th, 95th and 99th percentile curves, logarithmic scale (**a**), linear scale (**b**) are shown [120]. [rerif]



▶ **Fig. 4** Comparison of reference ranges (FMF UK vs. FMF D), 5th, 50th and 95th percentiles of FMF London (– –) with the percentiles of the FMF D (__) [121]. [rerif]

Nuchal translucency in trisomy 21, 18 and 13

If a combined first-trimester screening (FTS) is carried out, it *must* include the individual factors maternal age-related risk, NT, free beta-hCG and PAPP-A as an algorithm which combines these markers performs better than an algorithm based on only one marker.

(Level of recommendation A, level of evidence 2a, strong consensus 12/12)

Increased NT as a marker for structural malformations, genetic syndromes and other chromosomal disorders (▶ Table 3)

Invasive prenatal testing *should* be offered if NT is **3.0 mm**, at the very latest if NT is **>3.5 mm**.

If the cytogenetic analysis (DP, PCR, FISH) is unsuspicious, molecular genetic testing (e.g., microarray, trio exome sequencing) *should* be offered.

(DP: direct preparation of chorionic villi, PCR: polymerase chain reaction, FISH: fluorescence in situ hybridization)

(Level of recommendation B, level of evidence 2a, strong consensus 11/11)

▶ **Table 3** Nuchal translucency and chromosomal disorders, submicroscopic disorders and single-gene disorders [129].

		Congenital anomaly n (%)						
			Detected genetic anomaly (n = 636, 33.3%)					
			Chromosomal (n = 560, 29.4%)					
NT (mm)	All fetuses	All abnormal fetuses	Total	T21-18-13*	Other#	Submicroscopic‡	Single-gene disorders§	Structural (n = 178, 9.3%)
P95–P99	894 (47)	190 (21.3)	124 (13.8)	112 (12.5)	12 (1.3)	8 (0.9)	5 (0.6)	53 (5.9)
≥P99	1007 (53)	624 (62)	436 (43.2)	344 (34)	92 (9.1)	30 (3)	33 (3.3)	125 (12.4)
3.5–4.9	492 (26)	213 (43.3)	138 (28)	122 (24.7)	16 (3.2)	16 (3.2)	6 (1.2)	53 (10.8)
5.0–6.4	199 (10.5)	153 (76.8)	113 (56.8)	87 (43.5)	26 (13)	7 (3.5)	11 (5.5)	22 (11)
6.5–7.9	155 (8.2)	129 (83.2)	93 (60)	79 (50.6)	14 (9)	5 (3.2)	4 (2.6)	27 (17.3)
≥ 8.0	162 (8.5)	129 (79.6)	92 (56.7)	56 (34.4)	36 (22.1)	2 (1.2)	12 (7.4)	23 (14.1)
Total	1901	814 (43)	560 (29.4)	456 (23.9)	104 (5.4)	38 (2.0)	38 (2.0)	178 (9.3)

* Trisomy 21 (n = 272), Trisomy 18 (n = 134), Trisomy 13 (n = 50).

Other chromosomal disorders (detectable with classic karyotyping).

‡ Submicroscopic changes < 5 Mb detectable with microarrays.

§ DNA sequence variations which cause single-gene disorders, detectable with sequencing.

Additional risk markers: nasal bone, triuspid valve flow and ductus venosus flow

Nasal bone

Protocol for measurement of **Nasal Bone** (FMF London)

- The gestational period must be 11 to 13 weeks and six days.
- The magnification of the image should be such that the fetal head and thorax occupy the whole image.
- A mid-sagittal view of the face should be obtained. This is defined by the presence of the echogenic tip of the nose and rectangular shape of the palate anteriorly, the translucent diencephalon in the centre and the nuchal membrane posteriorly. Minor deviations from the exact midline plane would cause non-visualization of the tip of the nose and visibility of the maxilla.
- The ultrasound transducer should be held parallel to the direction of the nose and should be gently tilted from side to side to ensure that the nasal bone is seen separate from the nasal skin.
- The echogenicity of the nasal bone should be greater that the skin overlying it. In this respect, the correct view of the nasal bone should demonstrate three distinct lines: the first two lines, which are proximal to the forehead, are horizontal and parallel to each other, resembling an "equal sign". The top line represents the skin and bottom one, which is thicker and more echogenic than the overlying skin, represents the nasal bone. A third line, almost in continuity with the skin, but at a higher level, represents the tip of the nose.
- When the nasal bone line appears as a thin line, less echogenic than the overlying skin, it suggests that the nasal bone is not yet ossified, and it is therefore classified as being absent.

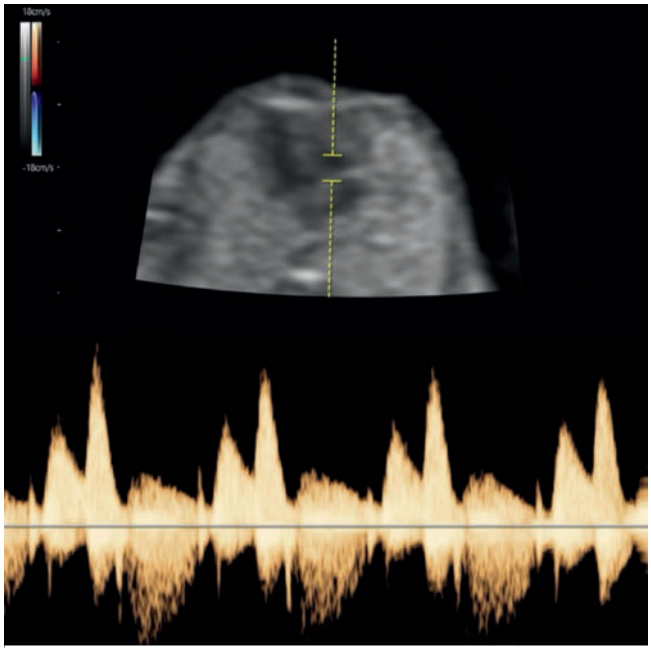
(Level of recommendation A, level of evidence 1b, strong consensus 12/12)

Tricuspid valve flow

Protocol for measurement of **Tricuspid Flow** (FMF London)

- The gestational period must be 11 to 13 weeks and six days.
- The magnification of the image should be such that the fetal thorax occupies most of the image.
- An apical four-chamber view of the fetal heart should be obtained.
- A pulsed-wave Doppler sample volume of 2.0 to 3.0 mm should be positioned across the tricuspid valve so that the angle to the direction of flow is less than 30 degrees from the direction of the inter-ventricular septum.
- Tricuspid regurgitation is diagnosed if it is found during at least half of the systole and with a velocity of over 60 cm/s, since aortic or pulmonary arterial blood flow at this gestation can produce a maximum velocity of 50 cm/s.
- The sweep speed should be high (2 – 3 cm/s) so that the waveforms are widely spread for better assessment.
- The tricuspid valve could be insufficient in one or more of its three cusps, and therefore the sample volume should be placed across the valve at least three times, in an attempt to interrogate the complete valve.

(Level of recommendation A, level of evidence 1b, strong consensus 12/12) (▶ **Fig. 5**)



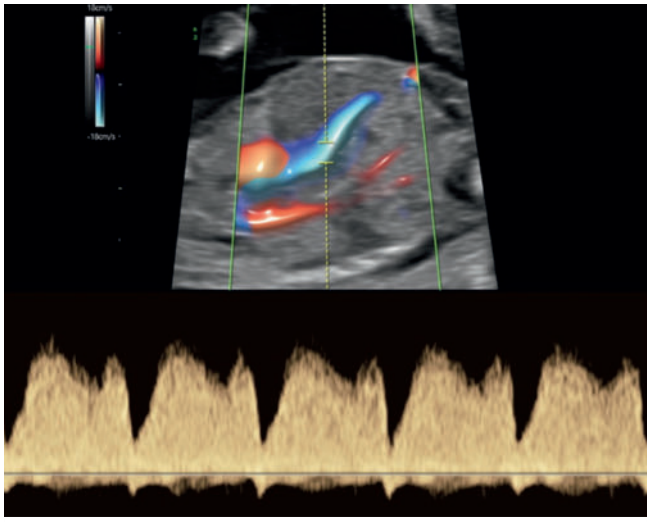
▶ **Fig. 5** Tricuspid valve flow. [rerif]

Ductus venosus flow

Protocol for measurement of **Ductus Venosus Flow** (FMF London)

- The gestational period must be 11 to 13 weeks and six days.
- The examination should be undertaken during fetal quiescence.
- The magnification of the image should be such that the fetal thorax and abdomen occupy the whole image.
- A right ventral mid-sagittal view of the fetal trunk should be obtained and color flow mapping should be undertaken to demonstrate the umbilical vein, ductus venosus and fetal heart.
- The pulsed Doppler sample volume should be small (0.5 – 1.0 mm) to avoid contamination from the adjacent veins, and it should be placed in the yellowish aliasing area.
- The insonation angle should be less than 30 degrees.
- The filter should be set at a low frequency (50 – 70 Hz) so that the a-wave is not obscured.
- The sweep speed should be high (2 – 3 cm/s) so that the waveforms are spread allowing better assessment of the a-wave.
- When these criteria are satisfied, it is possible to assess the a-wave and determine qualitatively whether the flow is positive, absent or reversed.
- The ductus venosus PIV is measured by the machine after manual tracing of the outline of the waveform.

(Level of recommendation A, level of evidence 1b, strong consensus 12/12) (▶ **Fig. 6**)



▶ **Fig. 6** Ductus venosus flow. [rerif]

The maternal serum markers free beta-hCG and PAPP-A *must* be adjusted for maternal weight, ethnicity, method of conception, smoking status, parity and chorionicity in multiple pregnancies.

(Level of recommendation B, level of evidence 2b, strong consensus 12/12)

No more than the two biomarkers (free beta-hCG und PAPP- A) *should* be used for risk calculation in combined FTS as more markers do not increase prediction.

(Level of recommendation B, level of evidence 2A, strong consensus 12/12) (▶ **Table 4**)

▶ **Table 4** Distribution of nuchal translucency and first-trimester serum biochemistry for trisomy 21, 18 and 13 [115].

	Euploid	Trisomy 21	Trisomy 18	Trisomy 13
Nuchal translucency (mm), median	1.2–2.5	3.4	5.5	4.0
Nuchal translucency > 95th percentile	5%	71.8%	74.8%	72%
Free beta-hCG (MoM), median	1.0	2.0	0.2	0.5
PAPP-A (MoM), median	1.0	0.5	0.2	0.3

An invasive procedure including molecular genetic analysis *must* be recommended if **PAPP-A** and/or **free beta-hCG** values are **<0.2** MoM or **beta-hCG** is **>5.0** MoM.

(Level of recommendation B, level of evidence 1b, strong consensus 12/12)

Screening accuracy for trisomy 21, 18 and 13

When screening for trisomy 21 in the general population, the combination of maternal age-related risk, gestational age, nuchal translucency and the serum markers free beta-hCG and PAPP-A (combined FTS) has the **highest accuracy** without performing cell-free DNA analysis and *should* therefore be the concept of choice.

(Level of recommendation A, level of evidence 2a, strong consensus 12/12)

After the patient has been given detailed information and counselling (GenDG), combined FTS *should* also be used to calculate the risks for trisomy 18 and 13.

The detection rate is around 95%.

The total FPR is only minimally increased by 0.1%.

(Level of recommendation B, level of evidence 1b, strong consensus 12/12) (▶ **Tables 5** and **6**)

▶ **Table 5** Accuracy of first-trimester screening [109].

Karyotype	Screen-positive rate (%)
Normal (n = 108 112)	4.6
Trisomy 21 (n = 432)	92.1
Trisomy 18 (n = 166)	96.4
Trisomy 13 (n = 56)	92.9

▶ **Table 6** Detection and false-positive rates for different cut-off values when screening for trisomy 21 in combined FTS [109].

Cut-off	Detection rate (%)	False-positive rate (%)
1:2	51	0.14
1:10	73	0.67
1:50	86	2.32
1:100	90	3.90
1:150	92	5.25
1:300	96	8.62
1:1000	98	19.26

Two-step screening with nasal bone, tricuspid valve or ductus venosus flow in cases of intermediate risk

If the risk calculation based on combined FTS determines that there is an intermediate risk of between 1:50 and 1:000, additional examinations *should* be offered.

This includes either investigation of the **nasal bone, ductus venosus flow** and **tricuspid valve flow** or **cfDNA** analysis.

The 2-step approach with **cfDNA** analysis for fetuses with an intermediate risk has a slightly higher detection rate and a considerably lower false-positive rate than the use of **additional ultrasound markers**.

(Level of recommendation B, level of evidence 2b, strong consensus 12/12)

5.6 Cell-free DNA analysis (cfDNA)

Fetal fraction

The ability to perform NIPT depends on the amount of fetal fraction in the cfDNA.

When carrying out cfDNA analysis, attention *should* therefore be paid to the quality parameter fetal fraction.

A common cut-off for FF is 4%; the laboratory *must* state the minimum threshold.

(Level of recommendation C, level of evidence 2c, strong consensus 12/12) (▶ **Table 7**)

▶ **Table 7** Detection factors affecting the fetal fraction (FF) [156].

Factors affecting the FF	Impact on the FF
***Fetoplacental* factors**	
Higher gestational age	increased
Increased crown-rump length	increased
Mosaicism	decreased
Aneuploidy	depends
Triploidy (digynic)	decreased
Multiple pregnancy	increased total FF, decreased FF per Fet
***Maternal* factors**	
Excess maternal weight	decreased
Autoimmune disease	decreased
Heparin	probably decreased
Elevated PAPP-A concentration	increased
Elevated beta-hCG concentration	increased
Ethnicity	depends
In vitro fertilization	decreased
Increased parity	decreased
Older maternal age	decreased

If the **fetal fraction** is below the **test-specific threshold value**, the cfDNA analysis will be inconclusive.

This usually occurs in **4%** of cases.

The examination *should* then be repeated after an interval of about 2 weeks.

In about 60% of cases, repetition of the examination generates a result.

(Level of recommendation B, level of evidence 2b, strong consensus 12/12)

If the cfDNA test is repeatedly **not analyzable,** this points to a higher risk of chromosomal disorders, especially trisomy 18, 13 and triploidy.

A diagnostic puncture or, alternatively, a repeat sonographic risk evaluation (combined FTS) *should* be carried out by an experienced fetal medicine specialist for further clarification.

(Level of recommendation B, level of evidence 2b, strong consensus 12/12) (▶ **Table 8**)

▶ **Table 8** Screening accuracy of cfDNA analysis for trisomy 21, 18 and 13 [167].

	Trisomy 21	Trisomy 18	Trisomy 13
Detection rate, % (95% CI)	98.8 (97.8–99.3)	98.8 (95.4–99.7)	100 (0–100)
False-positive rate, % (95% CI)	0.04 (0.02–0.08)	0.07 (0.03–0.17)	0.04 (0.02–0.08)
PPV, % (95% CI)	91.8 (88.4–94.2)	65.8 (45.3–81.7)	37.2 (26.1–49.9)
NPV, % (95% CI)	100 (99.99–100)	100 (100–100)	100 (100–100)

Irrespective of the technology employed, cfDNA analysis has a **detection rate** of **99%** for trisomy 21 and a **false-positive rate** of **0.1%**.

The detection rates for trisomy 18 and 13 are somewhat lower.

(Level of recommendation A, level of evidence 2a, strong consensus 12/12)

Despite the high **detection rates** and low **false-positive rates**, NIPT *must* be considered as a screening test, not as a diagnostic procedure to detect trisomy disorders.

Before an **abortion** is carried out, any positive test *must* be clarified further with an invasive diagnostic procedure.

(Level of recommendation A, level of evidence 2a, strong consensus 12/12)

5.7 Practical approach to different methods

Two-step model

After calculating the combined FTS risk, a cfDNA analysis *may* be carried out as part of a 2-step approach for intermediate risk cohorts.

This increases the test accuracy compared to the standard combined FTS.

(Level of recommendation A, level of evidence 1b, strong consensus 12/12)

▶ **Table 9** summarizes the relevant screening options and shows the screening accuracy for trisomy 21, 18 and 13.

▶ **Table 9** Screening options and screening accuracy for trisomy 21, 18 and 13 (modified from [2]).

Screening strategy	Description	DR/FPR (%)* Trisomy 21	DR/FPR (%) Trisomy 18/13
Combined FTS	MA+GA, fetal NT free β-hCG & PAPP-A for all patients Cut-off: **1:100** [109]	92/4.6 [109]	96.4 and 92.9 [109] (no increase in the FPR)
Combined FTS *intermediate* risk with additional US markers **NB, TR, DV**	Combined FTS with NB or TR or DV Risk **1:50–1:1000**	93–96/2.5 [111]	Trisomy 18: 91,8 [111] Trisomy 13: 100 [111] (no increase in the FPR)
Combined FTS *intermediate* risk with additional cfDNA analysis	Combined FTS with cfDNA analysis Risk **1:10–1:1000**	98.4/0.7 [171]	No data
NT and early screening for malformations with additional cfDNA analysis	NT and early screening for malformations followed by cfDNA analysis CVS if NT > 3.5 mm or malformations, otherwise cfDNA test failure = reflex test: (free β-hCG and PAPP-A)	100/0.1 + (additional 2.5% FPR if NT > 3.5 mm or malformations) [162]	Trisomy 18: 100% [162] Trisomy 13: 100% [162]

NT = nuchal translucency
MA = maternal age-related risk
GA = gestational age
NB = nasal bone
TR = tricuspid regurgitation
DV = ductus venosus flow
DR = detection rate
FPR = false-positive rate
CVS = chorionic villus sampling

5.8 No NIPT without FTS

The aggregated evidence shows that screening for a variety of problems of pregnancy @ 11–13+6 weeks of gestation is feasible, but only if the standard for screening as described in this guideline is strictly adhered to.

5.9 Screening for other chromosomal disorders using cfDNA analysis

Screening for rare and structural chromosomal disorders, microdeletions/duplications or monogeneic defects using cfDNA should currently **not** be recommended.

(Level of recommendation C, level of evidence 2b, strong consensus 12/12)

5.10 Screening for gonosomal chromosomal disorders using cfDNA analysis

Screening for **gonosomal** chromosomal disorders using cfDNA *should* currently not be unselective.

(Level of recommendation C, level of evidence 2, strong consensus 12/12)

5.11 Screening for rare autosomal trisomies using cfDNA analysis

Screening for **rare autosomal trisomies (RATs)** using cfDNA analysis *should* currently not be unselective.

(Level of recommendation C, level of evidence 2, strong consensus 12/12)

5.12 Screening for microdeletions/duplications using cfDNA analysis

The level of evidence regarding the validity of screening for **microdeletion 22q11** using **cfDNA analysis** is limited.

The limited significance of screening with regards to detection, the false-positive rate and prognostic validity *should* be part of the information provided to the pregnant woman and explained to her.

(Level of recommendation C, level of evidence 2, strong consensus 12/12)

5.13 Screening for structural chromosomal disorders (genome-wide screening) using cfDNA analysis

Screening for structural chromosomal disorders using cfDNA analysis should currently not be unselective.

(Level of recommendation C, level of evidence 2, strong consensus 12/12)

5.14 Summary

This summary clearly shows that focusing on common trisomies alone is not justified. The entire spectrum of chromosomal disorders should be taken into account, especially in younger patients. This applies both to possible screening examinations and to the verification of structural anomalies. This means that meaningful screening in the first trimester of pregnancy can only be based on detailed ultrasound examinations.

6 Quality Assessment and Audit @ 11–13^{+6} Weeks of Gestation

Attention *must* focus on the following **aspects in first-trimester screening:**

Current legal position regarding the prenatal evaluation of risks:

Counselling to be offered by the responsible physician (must be carried out by a physician)

- counselling **prior** to the examination: risk calculation vs. diagnostic tests
- written **consent**
- counselling **after** the examination

Quality: recognized state-of-the-art science and technology

- equipment employed for screening
- laboratory tests
- algorithm
- quality of reporting

Annual external quality assessment (of all diagnostic steps):

Ultrasound: **images, distribution of measured values** (comparison with reference values)

Laboratory tests

Algorithm

Overall performance

(Level of recommendation EC, RL, strong consensus 10/10)

(I) **Scoring systems** for image evaluation (qualitative)

(II) **Statistical methods** to evaluate the distribution of measured values (quantitative)

(III) Assessment of **overall performance**

The reproducibility of nuchal translucency measurements depends on training, standard levels, annual quality controls (ultrasound images and distribution of measured values, DR and FPR) and continuous individual feedback.

The detection rates published in studies can only be achieved if the FMF-UK criteria are adhered to (recommendations 5.2, ▶ **Fig. 1**).

The annual external audit *must* ensure that quality standards are met (recommendations 4.1–5, 5.2, ▶ **Fig. 1**)

(Level of recommendation A, level of evidence 1, strong consensus 10/10)

7 Screening for Preeclampsia and FGR @ 11–13^{+6} Weeks of Gestation

7.1 Screening for preeclampsia

Risk algorithms

Background risk (▶ Table 10)

▶ **Table 10** Risk factors for developing preeclampsia; pooled relative risk and 95% confidence intervals (95% CI); comparison with normal controls < 16 weeks of gestation, modified from Bartsch et al., 2016 [228].

Risk factor	Relative risk (RR)	95% CI
s/p PE	8.4	7.1–9.9
Chronic hypertension	5.1	4.0–6.5
Pregestational diabetes	3.7	3.1–4.3
Multiple pregnancy	2.9	2.6–3.1
aPL	2.8	1.8–4.3
Pregestational BMI > 30	2.8	2.6–3.1
SLE	2.5	1.0–6.3
s/p stillbirth (IUFD)	2.4	1.7–3.4
Pregestational BMI > 25	2.1	2.0–2.2
Nulliparity	2.1	1.9–2.4
s/p preterm placental abruption	2.0	1.4–2.7
Conception by ART	1.8	1.6–2.1
Chronic renal disease	1.8	1.5–2.1
Maternal age > 40	1.5	1.2–2.0
s/p FGR	1.4	0.6–3.0
Maternal age > 35	1.2	1.1–1.3

aPL: antiphospholipid antibody syndrome, ART: assisted reproductive technology, BMI: body mass index, IUFD: intrauterine fetal death, SLE: systemic lupus erythematosus, s/p: status post, PE: preeclampsia

Ultrasound

Doppler (▶ Table 11)

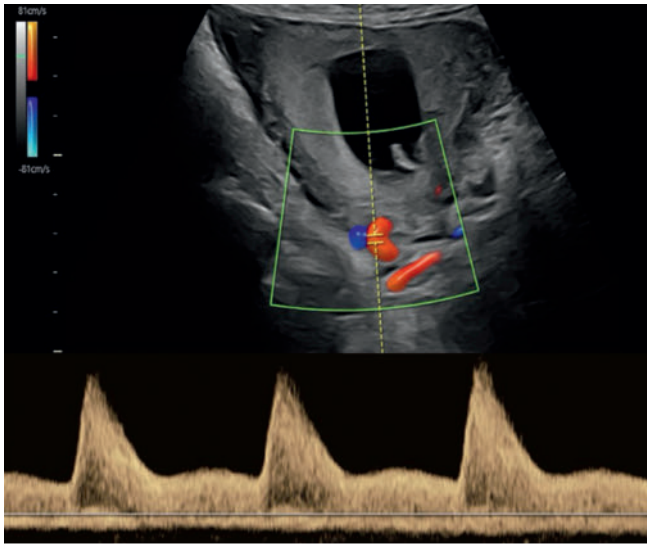
▶ **Table 11** Detection rates of preeclampsia screening in low-risk and high-risk pregnancies @ 11–13^{+6} weeks of gestation [231].

Doppler index	N	Sensitivity (95% CI) %	Specificity (95% CI) %	Pos. likelihood ratio (95% CI)	Neg. likelihood ratio (95% CI)
Total PE					
PI	4966	25 (20–31)	25 (20–31)	5.4 (4.1–6.7)	0.78 (0.72–0.84)
Bilateral notching	626	90 (73–98)	70 (66–74)	3.0 (2.4–3.3)	0.14 (0.05–0.36)
Uni/bilateral notching	869	93 (87–98)	46 (43–48)	1.7 (1.6–1.8)	0.16 (0.04–0.28)
Severe PE					
PI	433	40 (12–74)	90 (87–93)	4.0 (1.6–7.3)	0.67 (0.35–0.93)

Protocol for measurement of the **uterine artery PI** (FMF London)

- The gestational age must be between 11 weeks and 13 weeks and six days.
- Sagittal section of the uterus must be obtained and the cervical canal and internal cervical os identified. Subsequently, the transducer must be gently tilted from side to side and then colour flow mapping should be used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os.
- Pulsed wave Doppler should be used with the sampling gate set at 2 mm to cover the whole vessel and ensuring that the angle of insonation is less than 30°. When three similar consecutive waveforms are obtained the PI must be measured and the mean PI of the left and right arteries be calculated.

(Level of recommendation B, level of evidence 1b, strong consensus 12/12) (▶ **Fig. 7**)



▶ **Fig. 7** Doppler flow profile of the uterine arteries [237]. [rerif]

Biochemistry (▶ Table 12)

▶ **Table 12** Association of serum biomarkers with PE, pooled odds ratio and 95% confidence intervals (95% CI) for the occurrence of PE at any point in time during pregnancy ORs in decreasing order of magnitude [238].

Serum parameters	Odds ratio	95% CI
P-selectin (1 study)	6.36	2.53–15.98
Pentraxin (1 study)	5.31	1.88–15.01
PP 13	4.42	2.86–6.84
Inhibin A	3.57	1.68–7.61
VEGF (1 study)	2.44	0.99–6.0
PAPP-A	2.05	1.62–2.59
PLGF	1.94	0.8–14.67
sFlt-1	1.30	1.02–1.65
Endoglin	1.23	0.79–1.94
β-hCG	1.09	0.86–1.39

Biophysical examinations

Software algorithms

Every pregnant woman *must* be **offered preeclampsia screening** @ 11–13^{+6} weeks of gestation.

Preeclampsia screening @ 11–13^{+6} weeks of gestation *must* be carried out according to the algorithm of the Fetal Medicine Foundation.

Doppler scans of the uterine arteries *must* be carried out in accordance with the criteria of the Fetal Medicine Foundation UK.

(Level of recommendation A, level of evidence 1b, strong consensus 12/12)

7.2 Screening for FGR (no placental insufficiency)

Doppler (▶ **Table 13**)

▶ **Table 13** Detection rates of screening for fetal intrauterine growth restriction in low-risk or specific pregnancies @ 11–13^{+6} weeks of gestation, based on Doppler of the uterine arteries [231] (LoE 1a).

Doppler Index	n	Sensitivity (95% CI), %	Specificity (95% CI), %	Pos. likelihood ratio (95% CI)	Neg. likelihood ratio (95% CI)
Total FGR					
RI	1008	67 (35–90)	75 (72–78)	2.7 (1.6–3.5)	0.44 (0.18–0.81)
PI	3045	12 (8–16)	96 (95–96)	2.7 (1.9–3.8)	0.92 (0.88–0.96)
Bilateral notching	1420	74 (55–93)	42 (0–84)	1.3 (0.6–2.0)	0.62 (0.25–0.98)
Uni/bilateral notching	866	85 (80–91)	47 (45–50)	1.6 (1.5–1.7)	0.30 (0.19–0.42)
Severe FGR					
PI	999	24 (12–41)	95 (94–97)	5.3 (2.8–9.5)	0.79 (0.64–0.91)

Multifactorial screening

7.3 Screening for intrauterine fetal death

7.4 Prevention of preeclampsia and growth restriction

Pregnant women with a preeclampsia risk of > 1 : 100 @ 11–13^{+6} weeks of gestation, using the algorithm of the Fetal Medicine Foundation UK, must immediately receive treatment with Aspirin 150 mg every evening until week 36^{+0} of gestation.

(Level of recommendation A, level of evidence 1b, strong consensus 12/12)

8 Screening for Preterm Birth @ 11–13^{+6} Weeks of Gestation

8.1 Screening

Ultrasound

Cervical length

Cervical elastography

The detection rate for preterm birth based on vaginal ultrasound measurement of the cervix @ 11–13^{+6} weeks of gestation is 54.5 % (FPR 10 %) for a cut-off of 28 mm.

Elastography of the anterior lip of the cervix has a higher OR (53.8) than cervical length and width.

(Level of recommendation B, level of evidence 1b, strong consensus 11/11)

Biochemical markers

Pregnancy-associated plasma protein A (PAPP-A)

Free beta-hCG (f-βhCG)

Placental growth factor (PLGF)

Placental protein 13 (PP13)

Vitamin D

At 11–13^{+6} weeks of gestation, **PAPP-A, free beta-hCG, PLGF** and **PP13** have a low predictive value for preterm birth; the sensitivity of PP13 is 51 % and the specificity is 88 % (preterm birth before 37 weeks of gestation).

Vitamin D deficiency @ 11–13^{+6} weeks of gestation does not increase the risk of preterm birth.

(Level of recommendation A, level of evidence 1a, strong consensus 11/11)

Maternal and sonographic parameters

Maternal hemodynamics

Bacterial vaginosis

8.2 First-trimester prevention and therapy of preterm birth @ 11–13^{+6} weeks of gestation

Progesterone (vaginal, intramuscular, oral)

Pregnant women with a history of preterm birth, bleeding or a shortened cervix *may* be offered oral or vaginal micronized progesterone in the first trimester of pregnancy.

(Level of recommendation A, level of evidence 1a, strong consensus 11/11)

Aspirin

Cerclage

Early total cervical occlusion (ETCO)

Pessary

8.3 First-trimester screening for preterm birth in weeks 11–13^{+6} of gestation

9 Screening for Abnormally Invasive Placenta (AIP) and Placenta Accreta Spectrum (PAS) @ 11–13^{+6} Weeks of Gestation

9.1 Cesarean scar pregnancy and placental anomalies

9.2 Abnormally invasive placenta (AIP) and placenta accreta spectrum (PAS)

If screening for AIP/PAS @ 11–13^{+6} weeks of gestation is required, attention should be paid to the following parameters:

- cesarean section scar cannot be visualized
- interruption of the bladder wall
- thin retroplacental myometrium
- intraplacental lacunae
- retroplacental arterial-trophoblastic blood flow
- irregular placental vascularization

(Level of recommendation A, level of evidence 1b, strong consensus 11/11)

10 Screening for Velamentous Cord Insertion and Vasa Previa @ 11–13^{+6} Weeks of Gestation

10.1 Velamentous cord insertion and vasa previa

Cases with **low umbilical cord insertion** in the first trimester *should* undergo screening with vaginal ultrasound and color Doppler for vasa previa in the first trimester and early stages of the second trimester of pregnancy.

(Level of recommendation A, level of evidence 1b, strong consensus 11/11)

11 Screening for Diabetes Mellitus and LGA @ 11–13^{+6} Weeks of Gestation

11.1 First-trimester screening for abnormal glucose metabolism

11.2 Screening for GDM/iGDM @ 11–13^{+6} weeks of gestation

If **GDM screening** is carried out in the first trimester of pregnancy, testing *must* consist of a 75 g oGTT.

(Level of recommendation B, level of evidence 1b, strong consensus 10/10)

11.3 Screening for type 1 diabetes mellitus @ 11–13^{+6} weeks of gestation

11.4 Screening for LGA fetuses (non-diabetic) @ 11–13^{+6} weeks of gestation

LGA (macrosomia) screening in the first trimester of pregnancy should be carried out if:

- the mother has already given birth to a child with **macrosomia**
- other **risk factors** for **LGA** are present.

(Level of recommendation EC, strong consensus 10/10)

If **LGA (macrosomia) screening** is carried out in the first trimester of pregnancy, it must be based on maternal characteristics, NT, free beta-hCG and PAPP-A.

This approach identifies **35%** of LGA fetuses for a FPR of **10%**.

(Level of recommendation B, level of evidence 1b, strong consensus 9/9)

Starting in the first trimester of pregnancy, LGA (macrosomia) screening *may* be carried out based on **maternal factors** and serial **biometry**.

The inclusion of **biomarkers** does not increase the DR.

Screening based on maternal factors has a detection rate of **44%** and a FPR of **10%**.

If biometry is additionally carried out @ 19–24, 30–34 and 35–37 weeks of gestation, the respective detection rates are **51%, 56%** and **73%** with a FPR of **10%**.

(Level of recommendation B, level of evidence 2b, strong consensus 10/10)

11.5 Early intervention for GDM < 20 weeks of gestation

12 Important Research Questions

Gestational diabetes mellitus

13 Appendix

13.1 Ten golden rules for NIPT [355]

The German Society for Ultrasound in Medicine (DEGUM) has published recommendations for a balanced approach to cfDNA screening. They have been summarized under the heading “The 10 golden rules” [355].

They are:

1. NIPT requires that patients receive information and genetic counselling from a physician in accordance with the German Genetic Diagnosis Act (GenDG).
2. NIPT currently provides reliable risk estimations for the probability of trisomies 21, 18, 13 but no reliable statements about structural anatomical malformations. But these make up the majority of perinatally relevant anomalies. Most other chromosomal disorders and syndromal diseases cannot be detected by NIPT either.
3. NIPT requires an ultrasound examination, ideally prior to blood sampling and after 12 weeks of gestation.
4. In cases with sonographic evidence of malformations or increased nuchal translucency, invasive testing (CVS or amniocentesis) is the method of choice to detect chromosomal disorders and avoid unnecessary loss of time until the final diagnosis.
5. The fetal or pregnancy-specific percentage of cell-free DNA should always be reported in the NIPT examination. “Fetal fraction” is a quality parameter with a big impact on the test quality.
6. An inconclusive NIPT result needs further clarification. More chromosomal disorders are found in this cohort, especially trisomies 18 and 13 and triploidies.
7. NIPT is a screening test. If the NIPT results are abnormal, an invasive diagnostic test is obligatory. The indication for termination of pregnancy must not be based on isolated NIPT results alone.
8. NIPT for sex chromosomal disorders should not be routinely carried out.
9. The use of NIPT to determine the risk for rare autosomal aneuploidies and structural chromosomal disorders, especially microdeletions and monogenetic disease in the fetus, is currently not generally recommended.
10. NIPT has a higher failure rate in twin pregnancies, after assisted reproduction, and in patients with obesity, and data on test quality are limited.

13.2 Guide to abnormal NIPT [356]

The DEGUM has also published a basic guide on dealing with abnormal cfDNA results:

1. The legal framework

If the cfDNA test shows a higher risk for chromosomal disorders, it is important to follow the statutory requirements of the Act on Assistance to Avoid and Cope with Conflicts in Pregnancy (SchKG) and the German Genetic Diagnosis Act (GenDG). The cfDNA result must be passed on to the patient by the physician who arranged for the test. It must also be ensured that the pregnant woman receives information and genetic counselling about the test result promptly by a professionally trained and qualified physician.

2. An abnormal cfDNA test result is not a diagnosis

The cfDNA test for trisomy 21 is a screening test with a detection rate and false-positive rate of about 99% and 0.1% respectively. It should not be confused with the certainty provided by chromosomal analysis based on amniocentesis or chorionic villus sampling. The prevalence of trisomy 21 is 1:500, meaning that positive abnormal cfDNA test results are correct in only two thirds of cases. The positive predictive value is even lower if the disorder has a lower prevalence or the test quality is lower (e.g., sex chromosome abnormalities or structural chromosomal disorders). Further clarification based on invasive diagnostic testing should therefore be urgently recommended. Such testing is mandatory if a termination of pregnancy is being considered due to the abnormal test result.

3. The risk of fetal chromosomal disorders can be differentiated further by ultrasound screening

Structured early diagnostic screening for malformations must always be carried out after an abnormal cfDNA test. The risk for chromosomal disorders increases if the findings appear to indicate chromosomal abnormalities. The risk decreases again if sonoanatomy findings are unremarkable. The risk never sinks so low that invasive diagnostic testing to clarify the findings would not be justified.

4. The sonographic findings determine the method used for clarification

The pregnancy-specific DNA fragments evaluated by cfDNA analysis are primarily derived from the placenta. This needs to be taken into account when deciding on the type of invasive diagnostic test (amniocentesis or chorionic villus sampling). Chorionic villus sampling may be carried out if the ultrasound examination points to a specific chromosomal disorder. Amniocentesis should be done if the sonoanatomy findings are unremarkable or the constellation of findings is not clear, as in such cases it is necessary to evaluate the fetal cells.

5. Inconclusive cfDNA findings require further investigation

An inconclusive cfDNA test can have many causes. It is often due to maternal factors influencing the test results. But fetal chromosomal disorders must also be considered as a possible cause for the failed test. Structured early diagnostic testing for malformations should therefore be considered if the cfDNA test is inconclusive. Invasive diagnostic testing should be considered if malformations or signs of chromosomal disorders appear to be present. If the primary cause of test failure is a lack of sufficient pregnancy-specific DNA (fetal fraction, FF), the cfDNA test should be repeated after about two weeks with the expectation that by then, cfDNA analysis will be possible due to a natural increase in the FF. Invasive diagnostic testing should be discussed if the cfDNA test continues to be inconclusive.

14 Guideline Group Composition

14.1 Guideline coordinator/contact person

Guideline coordinator:

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14.2 Participating professional societies and organizations (▸ Table 14, Fig. 8)

▸ **Table 14** Members of the guideline group.

Mandate holders	Professional society/ organization	Period of involvement
Prof. Dr. Constantin von Kaisenberg	DEGUM	Entire period
Prof. Dr. Peter Kozlowski	DEGUM	Entire period
Prof. Dr. Oliver Kagan	DGGG	Entire period
Prof. Dr. Markus Hoopmann	DGGG	Entire period
PD Dr. Kai-Sven Heling	DGPM	Entire period
Prof. Dr. Rabih Chaoui	DGPGM	Entire period
Prof. Dr. Philipp Klaritsch	ÖGGG	Entire period
Prof. Dr. Barbara Pertl	ÖGUM	Entire period
PD. Dr. Tilo Burkhardt	SGUMGG	Entire period
Prof. Dr. Sevgi Tercanli	SGGG	Entire period
Dr. Jochen Frenzel	BVF	Until December 2022
Other participants	**Function and professional society/ organization**	**Period of involvement**
Dr. med Christine Mundlos	ACHSE	27 May 2023
Dr. Monika Nothacker	AWMF	Entire period

▸ **Fig. 8** Guideline group.

14.3 Patient/citizen participation

Dr. med. Christine Mundlos, M.Sc., Deputy Managing Director, ACHSE guide for physicians and therapists (Head of ACHSE Knowledge Network and Counselling) was approached and she attended the guideline session on chromosomal disorders held on 27 May 2023.

14.4 Methodological support

Methodological support during compilation of the guideline was provided by Dr. Monika Nothacker and Prof. Dr. Constantin von Kaisenberg, AWMF guidelines advisor.

15 Guideline Information

15.1 Methodology

The methodology used to compile this guideline is based on the AWMF Guidance Manual (Version 1.1, 27 Feb 2013).

Association of Scientific Medical Societies in Germany (AWMF) – Standing Guideline Commission. AWMF Guidance Manual and Rules for Guideline Development. 1st edition 2012; German-language version:
http://www.awmf.org/leitlinien/awmf-regelwerk.html

15.2 Systematic search and selection of evidence

The structures and headings of this guideline were taken from the "ISUOG Practice Guideline: performance of 11–14 week-ultrasound scan" and modified (Bilardo et al., 2023). The PICO questions were answered by carrying out a systematic search of the literature; identified studies were transferred to evidence tables. The evaluated quality of the studies was taken into account when compiling recommendations for action and background texts. A detailed description of the search for and selection of evidence is available in the guideline report for this guideline. The PICO questions are also listed there.

https://register.awmf.org/assets/guidelines/085-002m_S2e_Ersttrimester-Diagnostik-Therapie@11-13_6_Schwangerschaftswochen_2024-01_1.pdf

15.3 Critical evaluation of the evidence

The results of the analysis of various content points were summarized in tables. The templates corresponded to the models of the **G**rading of **R**ecommendations **A**ssessment **D**evelopment and **E**valuation (GRADE) international working group and the Guidelines International Network in its modified German version issued by the AWMF on 20 July 2011. The details of the evaluations of the respective subject areas are presented in the Method Report.

The evaluation of the evidence was done in accordance with the guidelines of the Centre for Evidence-Based Medicine of the University of Oxford (The Oxford 2011 Levels of Evidence). These guidelines include evaluation classifications for different types of studies. Our search used the evidence classification for *diagnostic* and **therapeutic** studies.

When evaluating *systematic reviews* and *meta-analyses*, particular importance was placed on the quality of the included studies. In cases where the authors had not carried out an evaluation following accepted guidelines (QUADAS, QUIPS, Cochrane, Newcastle-Ottawa, STROBE, AMSTAR etc.) themselves, the OXFORD criteria were used to evaluate the quality of the study. The sequence of the literature search is shown in a PRISMA flow diagram.

Randomized controlled clinical studies (RCTs) were evaluated in accordance with GRADE. Evaluations were grouped according to PICO questions/interventions. As far as possible, studies analyzed to address a specific PICO question were bundled according to outcomes. All RCTs were subjected to a GRADE evaluation, even if they were part of systematic reviews and meta-analyses.

In practice, only an evaluation according to the OXFORD criteria was done as practically all of the studies were diagnostic studies (▶ **Table 15**).

▶ **Table 15** Quality criteria (GRADE) for RCTs.

Quality criteria (GRADE) for RCTs	Content-related aspects
Risk of bias	▪ Lack of blinding ▪ Incomplete reporting (deviation from the protocol, drop-out of test subjects) ▪ Selective reporting of outcomes ▪ Early termination (< 200 dichotomous or < 500 continuous events) ▪ Non-validated methods for outcome collection (survey, surrogate endpoints) ▪ Recruitment bias (transfer of subjects between test groups) ▪ Transfer of effects in cross-over study designs
Inconsistency	▪ Broad distribution of measurement results between studies ▪ No overlapping of confidence intervals between studies ▪ Inconsistent significance values (marginal p-values)
Indirectness	▪ Different or heterogeneous study populations ▪ Different interventions ▪ Different clinical endpoints ▪ Indirect comparisons (e.g., to historical data, general population)
Imprecision	▪ < 300 dichotomous events, < 400 continuous events ▪ Too wide confidence intervals ▪ Did not achieve the calculated sample size (underpowered) ▪ Small sample sizes or low number of target events (e.g., mortality)
Publication bias	▪ Preliminary results ▪ Non-publication of negative results ▪ Publication in journals with a poor reputation

Cohort studies and observational studies were evaluated in evidence tables for the different PICO questions in accordance with the OXFORD criteria. Studies which were part of systematic reviews and meta-analyses were not assessed separately. The references for every PICO question were organized as follows: a) reference list of studies evaluated in evidence tables, and b) reference list of studies analyzed in systematic reviews and meta-analyses.

15.4 Achieving consensus

Participants pre-voted on recommendations for action and background texts in an online voting procedure. If the consensus was > 95 %, no further voting occurred. If this was not the case, another round of voting was carried out under neutral moderation during an online or in-person meeting.

15.5 Grading of recommendations and determination of the strength of consensus

Determining the level of recommendation

Recommendations are graded on the basis of methodologically synthesized evidence, clinical expertise and patient preferences. Other criteria additionally taken into account for the grading of recommendations are: consistency of study results; clinical relevance of the endpoints and effect sizes; benefit-to-harm ratio; ethical, legal, economic obligations; patient preferences; applicability to the patient target population and the German healthcare system, practicability in routine clinical practice/in different areas of care.

▶ **Table 16** shows the grading used for the recommendations presented in this guideline.

▶ **Table 16** Example 1: Three-level grade system for recommendations.

Level of recommendation	Description	Expression	Symbol (facultative)
A	Strong recommendation	must/ must not	⇑⇑/⇓⇓
B	Weak recommendation	should/ should not	⇑/⇓
0	Open recommendation	may/ may not	⇔

Determining the strength of consensus

The strength of consensus was classified as shown in ▶ **Table 17**.

▶ **Table 17** Establishing the strength of consensus.

Classification of the strength of consensus	
Strong consensus	> 95 % of participants agree
Consensus	> 75–95 % of participants agree
Majority agreement	> 50–75 % of participants agree
No majority agreement	< 50 % of participants agree

16 Editorial Independence

16.1 Financing the guideline

The DEGUM has provided this guideline with funding amounting to € 25 000 and the DGGG has supported it with € 5000.

This money was used almost exclusively to carry out the systematic search of the literature and the evaluation of evidence.

Travel expenses to attend in-person meetings in DEGUM's representative office were paid for by the professional medical society sending the mandate holder(s).

16.2 Description and management of conflicts of interest

All members of the guideline group submitted a conflict of interest disclosure. Please refer to Appendix 5 Conflict of Interest (Table on the disclosure of interests and management of conflicts of interest) in the Method Report.

The conflict of interest disclosures were discussed and assessed by Dr. Monika Nothacker and the guideline coordinator Prof. Dr. Constantin von Kaisenberg.

As regards the thematic relevance to the guideline, lectures to industry were categorized as low (limits to taking on a leading role), consultant and reviewer work/third-part funding for research as moderate (abstention from voting) and proprietary interesdt such as patents or working mainly for industry as high (no participation in thematically relevant consultations and no vote). No COI: 5/12; low COI: 6/12; moderate COI: 2/12; high: 0/12.

Protective factors which can counteract bias arising from conflicts of interest include a pluralistic composition of the guideline group, a structured process to achieve consensus under neutral moderation, a discussion about interests and the management of conflicts of interest at the start of the consensus conference, and a public version for consultation.

17 External Evaluation and Adoption

An external evaluation was done in the form of a public consultation over a period of four weeks on the website of the AWMF. After the deadline had expired, all comments which had been sent in were read and considered. If new studies and high-quality evidence were presented, the recommendations for action/background texts were discussed again by the guideline group and amended where necessary. This process is also discussed in the Guideline Report.

The guideline was adopted during the period from 1 October 2023 to 31 December 2023 by the executive boards of the participating professional societies.

18 Period of Validity and Update Procedure

This guideline is valid from 1 January 2024 through to 31 December 2028 (5 years). Regular updates are planned; if an amendment is urgently required, it will be published separately. Comments and advice on the update procedure are expressly welcomed and can be sent to the guideline secretariat.

Note

The guideline will be published simultaneously in the official journals of both professional societies (i.e., Geburtshilfe und Frauenheilkunde for the DGGG and Ultraschall in der Medizin/European Journal of Ultrasound for the DEGUM).

Conflict of Interest

See also the long German-language version of the guideline: https://register.awmf.org/de/leitlinien/detail/085-002

References

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