The role of ultrasound in first-trimester screening after the introduction of NIPT as a service of public health insurance – a consensus statement of the Fetal Medicine Foundation (FMF) Germany

Die Rolle des Ersttrimester-Screenings nach Einführung von NIPT als Kassenleistung. Ein Konsensus-Statement der Fetal Medicine Foundation (FMF) Deutschland

Introduction

For two decades, combined first-trimester screening (FTS), including data on maternal age, ultrasound markers, and biochemical parameters, had been the most reliable noninvasive procedure to calculate the risk of chromosomal abnormalities between 11+0 and 13+6 weeks of gestation [1, 2, 3, 4, 5]. The introduction of noninvasive prenatal tests by sequencing cell-free placental DNA has been proven to be reliable noninvasive procedures to detect the most common chromosomal abnormalities (trisomies 21, 18, 13) in the first trimester. The aim of this paper is to demonstrate the strengths and limitations of these two procedures and to give a consensus statement of the Fetal Medicine Foundation (FMF) Germany on how to use the two techniques in the first trimester after the introduction of NIPT as a service of the statutory health insurance companies in Germany.

ZUSAMMENFASSUNG

Das kombinierte Ersttrimester-Screening und der nichtinvasive DNA-Test (NIPT) haben sich als verlässliche nichtinvasive Verfahren zur Diagnostik der häufigsten Chromosomenanomalien (Trisomie 21, 18, 13) im 1. Trimenon gezeigt. Das Ziel dieser Publikation ist es, die Stärken, wie auch die Limitierungen, beider Verfahren aufzuzeigen und ein Konsensus-Statement der Fetal Medicine Foundation (FMF) Deutschland abzugeben, wie beide Techniken im 1. Trimenon eingesetzt werden sollen, nachdem NIPT als Kassenleistung in Deutschland eingeführt wurde.
Merk E et al. The role of "ents-to-be with accurate information about their fetus. Undoubtedly, cell-free fetal DNA screening in maternal blood (NIPT) is currently the best noninvasive screening test for assessing the risk of trisomies 21, 18, 13 and sex chromosomal abnormalities [26], and it also has some value in assessing the risk of 22q11.2 deletion syndrome [28, 29]. However, NIPT is still an advanced screening test and not a diagnostic test. It may be limited by its moderate low positive predictive value, especially for conditions with low prevalence in the tested population. Furthermore, the test has several limitations (see Table 5) and requires qualified genetic...
Merz E et al. The role of NIPT in public-health-based programs allows two different application models: 1. NIPT as a first-line screening tool (effectively replacing conventional serum and NT screening) [38, 39] or 2. NIPT as a second screening step (contingent screening model) in the case of an abnormal FTS result [38, 40]. The advantages of NIPT for first-line screening are the simplicity of the procedure and the fact that there is no need for specialized training besides qualifications in prenatal counseling.

counseling prior to the test and after the test result is available (German Gene Diagnostics Act [37]).

The implementation of NIPT in public-health-based programs allows two different application models: 1. NIPT as a first-line screening tool (effectively replacing conventional serum and NT screening) [38, 39] or 2. NIPT as a second screening step (contingent screening model) in the case of an abnormal FTS result [38, 40]. The advantages of NIPT for first-line screening are the simplicity of the procedure and the fact that there is no need for specialized training besides qualifications in prenatal counseling.

However, it is only a test for trisomies 21, 18, and 13 and sex chromosome abnormalities and, if performed without any ultrasound examination, no structural abnormalities or other genetic anomalies can be detected. Contingent screening using FTS with a qualified fetal anatomy scan first allows exclusion or detection of structural defects and – after risk assessment – differentiation between high-risk, intermediate-risk and low-risk groups [5, 41]. If there is normal sonoanatomy and the risk assessment shows a result in the intermediate or low-risk group, NIPT can be performed as soon as the FTS risk assessment is available or, alternatively, NIPT can be performed directly after the FTS anatomy scan has shown normal sonoanatomy and the risk assessment shows a result in the intermediate or low-risk group. NIPT is not recommended, and invasive testing should be performed instead. However, the enactment of a contingent model requires an already well-established national screening program based on combined first-trimester screening including NT measurement and serum biochemistry [38]. In all countries where a qualified and standardized ultrasound examination and a qualified FTS AUDIT are guaranteed (such as with FMF UK or FMF Germany [5, 41], a contingent screening [40, 42, 43] seems to be the preferred approach.

With the introduction of NIPT as a service covered by the statutory health insurance companies in Germany – while FTS is still a service for self-payers – a tremendous increase in NIPT and a decrease in FTS could be observed [44] (Fig. 2).

NIPT, performed as first-line screening without any prior ultrasound examination, does not allow the detection of any fetal structural malformations, early fetal growth restriction, twin abnormalities, or abnormal placental structure. In contrast, qualified combined first-trimester screening with a detailed ultrasound ex-
amination allows the detection of the most common trisomies, triploidy, and the demonstration or exclusion of various structural defects (▶ Table 3). As early prenatal screening provides more than just risk assessment of trisomies 21, 18 and 13, every pregnant woman should receive comprehensive information about current noninvasive and invasive procedures and early pre-eclampsia screening [22, 23, 46, 47].

There is broad consensus in several ultrasound societies and publications that a detailed first-trimester ultrasound examination should always be performed prior to an NIPT procedure [40, 47, 48, 49, 50, 51, 52].

Since NIPT has been covered by statutory health insurance since July 1, 2022, NIPT will become more popular and FTS biochemical screening, which is subject to a fee, will continue to decline. The hormone parameters free β-HCG and PAPP-A will no longer have the importance they had in pre-NIPT times, but they may continue to be offered as an option, or in situations where NIPT is not recommended (e.g., vanishing twin) or in cases with very low fetal DNA fractions. On the other hand, PAPP-A is a biomarker that is also used in pre-eclampsia screening in the first trimester [23].

As a result, FMF Germany recommends performing NIPT as a contingent procedure, either once the FTS results are available (▶ Fig. 3) or directly after the FTS ultrasound examination has shown no structural fetal malformation and normal NT (▶ Fig. 4).

Conclusion

While NIPT is currently focusing on screening for trisomy 21, 18, 13 and sex chromosomal abnormalities only, combined first-trimester screening with a detailed ultrasound check of the fetal anatomy is of major importance for the early detection of structural defects. Consequently, NIPT should not replace combined first-trimester screening with a detailed check of the fetal morphology. Therefore, the optimal first-trimester screening approach would be to first perform a detailed ultrasound examination and a risk calculation with the basic parameters of maternal age, crown-rump length, and nuchal translucency thickness, and – for experienced operators – with the additional ultrasound parameters absence/presence of nasal bone, ductus venosus flow, and tricuspid regurgitation. If no structural abnormality is found and the risk assessment shows a result in the low-risk or intermediate-risk group, NIPT can be performed for advanced screening for trisomies 21, 18, 13 and sex chromosome aneuploidies. If a structural abnormality is detected during the ultrasound examination, NIPT is no longer advisable and instead, CVS or an amniocentesis should be performed for karyotyping (▶ Fig. 3).
as well as microarray [53] and genome sequencing [54, 55] if required.

Finally, the key statements for early prenatal screening are listed in ▶ Table 6.

Conflict of Interest

The authors declare that they have no conflict of interest.

References


