Early
Prenatal Diagnosis –

New Advances in
Early Pregnancy Care

The 11-14 Week Scan

First-trimester screening allows an assessment of the risk for chromosomal abnormalities and/or other fetal diseases at the earliest possible time.

FMF
DEUTSCHLAND

The Certified Procedure

1. Prerequisites

Prior to performing first-trimester screening, physicians must inform their pregnant patients properly. They are required to provide individual counselling and to obtain their patients' consent to the screening procedure. Patients must be informed about the quantitative risk of spontaneous abortion in the first trimester of gestation in relation to the respective screening method chosen and in view of its possible impact. Pre-screening consultation is in the sole responsibility of the certified gynaecologist.

2. Ultrasound markers

Sonographic parameters are able to detect fetal chromosome abnormality not until the second trimester of gestation, whereas nuchal translucency measurement (briefly called NT) provides a highly sensitive screening marker as early as between weeks 11 and 14. NT measurement always has to be performed in conjunction with crown-rump length measurement (CRL). Low nuchal translucency has to be considered physiological. However, as nuchal translucency diameter increases, so does the likelihood of a fetal chromosomal abnormality (e.g. chromosomal aberration, cardiac defect). In the event of significantly increased NT, the pregnant patient should receive further counselling so that a specific procedure can be discussed and agreed upon. Approximately two-thirds of the fetuses affected by trisomy 21 can be assigned to a risk group at an early stage of gestation thanks to NT measurement and consideration of maternal age.

However, NT is also an important marker to detect other non-chromosome disorders, such as cardiac defects, hypoproteinaemia, lymphatic hypoplasia, and skeletal anomalies, for which reason NT measurement assumes special significance.

In order to ensure a uniform quality standard, NT measurement must be carried out according to the guidelines of the FMF-Germany. It is also pointed out that the sonographic service goes beyond NT measurement and that it includes a structured search for further sonographically suspect findings. Patients should not only be informed about the option of first-trimester screening, but also about the possibility of having a further ultrasound examination ("organ

diagnosis") to be performed between 18 and 22 gestational weeks.

3. Biochemical markers

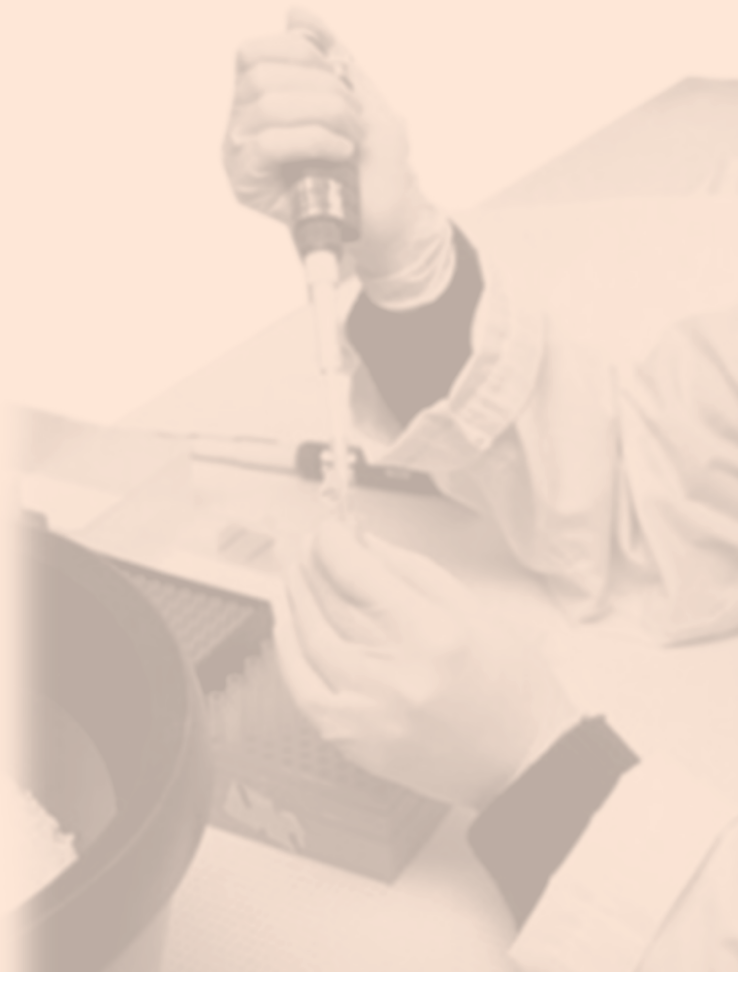
PAPP-A (pregnancy-associated plasma protein A) and free beta-hCG are the most suitable biochemical serum markers for detection of fetal chromosome disorders in the first trimenon of gestation. The optimum time for blood collection is the period between weeks 11 and 13 of gestational age. During this time, measurement of crown-rump length (CRL) is also mandatory for the determination of gestational age. It allows a reliable assignment of biochemically determined values to gestational age.

About two-thirds of all trisomy 21 pregnancies can be assigned to a risk group by means of biochemical markers in combination with maternal age.

Since free beta-hCG is thermolabile, no whole-blood samples should be submitted. If temperatures exceed 25°C, all samples will have to be refrigerated. Measurement of biochemical parameters has to be based on an evaluated system of analysis. The "Kryptor" system of B.R.A.H.M.S AG is currently the only platform which has proven its ability to meet those high requirements posed on measurement accuracy. Therefore, it must be considered a laboratory reference system.

4. Combination of serum and ultrasound parameters

According to previous studies, a combined risk assessment based on PAPP-A and free beta-hCG values as well as on sonographic NT measurement in the first trimenon leads to a 89 percent detection rate of trisomy 21. Risk calculation must be carried out by means of licensed evaluation programmes that are based on the algorithm of the FMF-Germany.



5. Post-screening counselling of pregnant patients

The disclosure of results after first-trimester screening is of special importance. It requires a high degree of empathy on the part of the counsellor in his or her dialogue with the pregnant patient. The gynaecologists certified by the FMF-Germany are responsible for providing proper consultation in this respect. Special genetic counselling is offered by certified human geneticists. Since more than 40 percent of all pregnancies with fetal trisomy 21 result in spontaneous abortion between the 10th week of gestation and the date of delivery, every certified risk report should contain an information to this effect for pregnant women.

6. Prerequisites for the performance of first-trimester screening

Since qualified NT measurement is of greatest relevance in the assessment of the risk for chromosomal disorders, these should be performed solely by sonographers certified by the FMF-Germany. Meticulous NT measurement with the help of a high-resolution ultrasound device (= 5

Supplementary Information:

Following genetic counselling, two invasive measures may be considered: either chorion villus sampling after 10 weeks of gestation, or amniocentesis from week 14 onward with fast partial karyotyping through FISH mapping (Fluorescence In Situ Hybridisation) or PCR (Polymerase Chain Reaction).

If chromosome analysis shows an unsuspicious karyotype despite suspicious nuchal translucency values, pregnant women must be informed about other possible causes of increased nuchal translucency, and further ultrasound examinations must be offered.

Risk assessments related to neural tube defects by serum AFP assay are not possible at this early stage and might have to be established after another blood collection.

MHz) is required to this end. Centres as well as gynaecologists in independent practice who use the NT value as a risk parameter have to adhere strictly to the guidelines established by the FMF-Germany. Each examiner should have obtained the corresponding certification from the FMF-Germany as the primary prerequisite.

The high quality of results obtained from the measurement of biochemical markers is ensured by laboratories which are particularly qualified in this field and which have achieved special certification.

The certification process as well as ongoing quality monitoring is the responsibility of the FMF-Germany.

All certified laboratories are under the obligation to solely use those calculation programmes for risk calculation which have been licensed by the FMF-Germany. Furthermore, the certified laboratories must participate in an external interlaboratory trial (currently UK-NEQAS). All certified laboratories undertake to deliver their risk evaluations in a uniform manner and only to certified gynaecologists. They also undertake to submit data obtained in the framework of first-trimester screening on to the FMF-Germany.

The measures described above ensure an exemplarily high quality standard in the performance of first-trimester screening, which is to the benefit of the pregnant patient.

7. Further training and transitional periods

In order to make FMF-compliant first-trimester screening available country-wide, a transitional period was created which lasted until 31st December 2002 and during which gynaecologists in the process of certification were given the opportunity to participate in the first-trimester concept described above.

Since 1st January 2003, only certified gynaecologists have received certified result reports in cooperation with corresponding laboratories. Only those colleagues who were in the certification process (e.g. who had successfully completed the FMF-certified theoretical course) received the evaluation programme during the transitional period (i.e. from 1st April 2002 to 31st December 2002) until 31st December 2002. Since that time, renewal has been confined to those colleagues who have successfully completed the entire FMF German-language certification process.

The FMF-Germany aims at establishing qualified first-trimester screening by certified gynaecologists

fast and country-wide. At the same time, well-targeted media work is designed to inform pregnant women as comprehensively as possible about the advantages of this “high-quality screening method”.

FMF-Germany

Various interdisciplinary groups of leading gynaecologists, laboratory physicians, human geneticists and application-focused companies have associated in 2002 to explore and discuss possibilities for prenatal risk assessment in regard to fetal chromosome anomalies and other diseases that may develop in the first third of pregnancy (First-Trimester Screening). This group has given rise to the Fetal Medicine Foundation (FMF) Germany – an interdisciplinary charitable association aiming to promote research and training in prenatal medicine. The members of the Fetal Medicine Foundation Germany feel bound by self-obligation to ensure the best possible standard for the introduction of first-trimester screening in Germany, right from the very start. This requires a high level of standardisation in diagnostic procedure to be implemented under strict scientific quality control. All institutions and individuals involved have agreed to pursue a uniform test concept in their performance of first-trimester screenings from the first of April 2002 onward. The same procedure is demanded by the scientific advisory board of the German Federal Medical Association in its guidelines on the prenatal diagnosis of diseases and disease predispositions.

There is broad consensus that the internationally evaluated procedures of the Fetal Medicine Foundation (FMF) London and of the DEGUM (German Society of Ultrasound in Medicine) should serve as guidelines for the establishment of first-trimester screening. Their shared goal is the area-wide and fastest possible establishment of first-trimester screening in Germany – certified and controlled by the FMF-Germany / DEGUM. The same standard is poised for introduction in the German-speaking countries of Austria and Switzerland, in cooperation with the ÖGUM (Austrian Society of Ultrasound in Medicine) and the SGUM (Swiss Society of Ultrasound in Medicine). Moreover, an evaluation of future strategies in prenatal diagnosis is envisaged, and so is reliable and ongoing contact with the press, as well as with self-help groups and hence with women in pregnancy.

At end-2001, the FMF London, represented by Kypros Nicolaides, has transferred both the training and the certification mandate to the FMF-Germany, represented by Prof. Eberhard Merz.

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