Early Prenatal Diagnosis –

New Advances in Early Pregnancy Care

In the framework of a scientific round-table meeting, the managing board of the FMF-Germany has formulated the principles, goals and, not least, the importance of both the Organisation and of first-trimester screening within prenatal medicine and obstetrics. At the same time, participants in the meeting presented their visions and wishes with respect to the future shape of certified, high-quality procedures in prenatal diagnosis.

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Prof. Dr. med. B.- Joachim Hackelöer
Head Physician of Prenatal Diagnosis and Therapy,
General Hospital Barmbek

„My vision is to bring to an end the practice of gross generalisation and risk imposition on pregnant women. Now we make it possible for a pregnant woman to freely determine how much she wants to know about the risk to her pregnancy."

The State of the Art in Prenatal Diagnosis in Germany

Prof. Dr. med. B. -Joachim Hackelöer

All in all 1.2 million pregnancies in Germany account for about 800,000 births, whereby the birth figure is tending to decline over time. Approximately 12,000 gynaecologists are engaged in independent practice, and another 6,000 are clinic-employed gynaecologists. All of them encounter first-trimester screening in one form or another, i.e. by either self-performing the examinations it involves or by arranging for them to be performed.

The official figure of induced abortions in Germany amounts to roughly 15,000; the number of unreported cases of abortion is estimated at up to 200,000. Although there are no exact or documented figures, we can safely assume that less than one percent of all pregnancy terminations per year (this corresponds to approximately 1,000 abortions) are carried out as a result of prenatal diagnosis, i.e. because of ultrasound-detected chromosomal disorders or malformations.

With regard to ultrasound, three examinations are mandatory in the framework of prenatal care screening. One of them concerns the first trimester. Mandatory health insurance benefits under the RVO ("German Reich Insurance Code", also referred to as "Imperial Insurance Regulation") cover an average of six examinations per pregnancy, two of which must usually be performed during its early stage. Then there are the examinations carried out in private practice which are not covered by the RVO benefits and which amount to approximately 10 to 20% of the overall figure. This adds up to about 6 to 9 million annual ultrasound examinations in Germany, of which 2 to 3 million are performed during the first trimester of pregnancy. The number of possible NT measurements amounts to approx. 1 million per year. In Germany, the acceptance of ultrasound diagnosis is estimated at 90 percent.

One quality standard in German prenatal diagnosis is the official "mother's passport". As we all know, this passport only represents a minimum quality standard. But at least it prescribes the scope of ultrasound examinations. The second quality standard is the already known multiple-level concept of the DEGUM. About 500 to 600 gynaecologists are Level I certification holders, and it can be well assumed that a large number of non-certified medical practices also meet the DEGUM I standard. The DEGUM Level II standard can be narrowed down with greater precision because it is already subject to review, whereby the monitoring process itself also receives ongoing control. Approximately 500 gynaecologists are certified at this level, whereas 30 gynaecologists hold a DEGUM Level III certificate. The third existing quality standard is the FMF-England with approx. 200 certified gynaecologists in Germany. To this add two prenatal care divisions at universities or clinics, 18 further, non-independent divisions with accredited physicians, about 10 officially approved specialist medical practices with several physicians focusing on prenatal care, as well as 5 to 10 clinics where the respective principal provides approved prenatal consultation services on a regular basis.

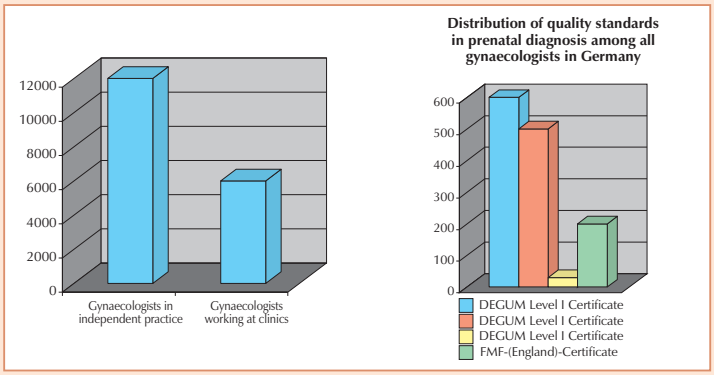
The problem is, however, that the quality controls demanded by the German association of panel doctors do not work. DEGUM levels, by contrast, are a quality control device because their validity is restricted to a specific period of time, i.e. five years. Moreover, DEGUM Level II now also comprises an oral examination which constitutes an additional control tool. At the FMF-England, quality monitoring is conducted via the AUDIT.

The number of additional ultrasound examinations that are performed besides ordinary prenatal care are legion in Germany because approximately 90 percent of all pregnancies there are identified as risk pregnancies (as per entries in mother's passports). These additional examinations are further ultrasonographical investigations in terms of differential diagnosis (malformation diagnosis), Doppler examination and fetal echocardiography. The health care system thus incurs an estimated overall 100 million Euro plus the cost of ordinary prenatal care. The cost created by unnecessary invasive interventions defies reliable estimation. However, we assume that approx. 70,000 pregnant women aged 35 and over are concerned per year. These are all cost factors which might be reliably reduced through qualified, non-invasive pre-diagnosis, for instance, in the form of first-trimester screening.

Let us finally take a look at screening results in terms of quality: At Level I, 20% of examiners are able to detect diseases or fetal malformations; at Level II, 45 % are skilled to do so; at Level III even 95%. It must be pointed out that the rate of perinatal mortality has decreased continuously; the current figure is about 6 per mil. The rate of premature deliveries, however, has remained unchanged.

With all this said, the following facts can be established in regard to quality assurance in Germany:

- Both the quality tools and the potential required in order to implement the desired modalities exist.
- At present, quality assurance is being implemented only in part and is therefore exposed to strong criticism from non-medical groups and individuals. They consider prenatal diagnosis in its hitherto practice a mere tool devoted to the singling out of "unworthy" life – a tool imposed on women and depriving them of their freedom to decide. The only quality assurance systems available so far used to be those established by the DEGUM and the FMF-England.
- Costs incurred by the health care system can be substantially reduced by quality-assured screening processes in the first trimester of gestation.



Prof Dr.med. Rüdiger Osmers
Head Physician at the Gynaecological Clinic, City Hospital, Hildesheim

„I hope that the FMF-Germany will manage to present its goals convincingly – both to the medical and the non-medical community – by improving the overall quality in prenatal diagnosis and by achieving a substantial reduction of invasive interventions in the first trimenon. In the long term, this improvement may open the way for a further development of goals and responsibilities for the second and third trimenon, which might then become a further primary concern".

The Philosophy of the FMF-Germany

Prof. Dr. med. Rüdiger Osmers

The establishment of the FMF-Germany is something very special – in all respects. Gynaecologists, prenatal diagnosticians, laboratories, human geneticists, software manufacturers, and, not least, industrial communities have joined forces for the first time ever to create innovative mutual ties - under the guardianship of the English parent association FMF-London.

The foundation of the FMF-Germany was not meant to create new patient examinations for the first trimester of gestation. The order of the day was, rather, to raise already existing methods to a qualitative standard which would do justice to all involved, especially to pregnant women with their individual pregnancies. This is done in close cooperation between the FMF-Germany and the already existing DEGUM system – a quality assurance tool used in prenatal diagnosis.

Throughout the German-speaking countries, the FMF-Germany is engaged in interdisciplinary cooperation with Austria and Switzerland. Nuchal translucency measurement and biochemical parameter determination are used to ensure that the following essential issues are given constant priority: first, the improvement of prenatal care, particularly in the first trimenon of pregnancy, with the help of the afore-mentioned interdisciplinary network; second, the establishment of an interdisciplinary quality management certification process for laboratories and gynaecologists, aided by certified software tools. This allows to reduce the number of invasive interventions during pregnancy, and at the same time brings improved examination quality.

Besides this focus, the FMF-Germany strives to promote scientific development. The creation of a central data base in Germany will not only contribute to maintaining already achieved quality standards, but will also help attain substantial long-term quality improvements in prenatal diagnosis – well beyond the next decade.

The FMF-Germany is thus also bestowed with a number of other tasks: first, with the task of providing regular further training courses to colleagues in independent practice and to laboratories; second, of implementing a performance-oriented certification process; and, third, of arranging for quality controls, so-called AUDITS, which their certified colleagues in independent practice are required to undergo in regular intervals.

This ensures not least an ongoing qualitative and scientific development in prenatal care so that the foundation of the FMF-Germany in itself is the basis, the very foundation, as it were, of an interdisciplinary quality management system in prenatal care which is not confined to Germany, but, for the first time ever, has Europe-wide reach and realm.

The Goals of the FMF-Germany

Prof. Dr. med. Eberhard Merz

The FMF-Germany strives at providing the 11-14 week scan with a defined performance standard to all pregnant women throughout Germany.

The scope of services supplied to pregnant women comprises a qualified ultrasound examination of the fetus between weeks 11 and 14 of gestation, i.e. performance of the so-called nuchal translucency measurement, as well as maternal blood collection in order to determine the parameters PAPP-A and free beta-hCG. In contrast to previous screening methods, which every physician was allowed to perform without specific knowledge, this method is based on a defined standard of performance.

This standard is achieved through a certification process. It requires the successful completion of a training course which is comprised of a theoretical and a practical examination. The certification procedure was largely adopted from the parent association FMF-London, whereby it was adjusted to German conditions. Physicians who have passed through this certification process are authorised by the FMF-Germany to perform the 11-14 week scan including risk evaluation. In order to maintain the achieved quality standard, every certified gynaecologist undertakes to participate in a quality assurance programme, the so-called AUDIT. This quality assurance programme provides for regular submissions of certain measurement values and ultrasound images to the FMF-Germany. This must be done in 12-month intervals. If the review of measured values and/or ultrasound images reveals that they are of sub-optimal quality, recertification will be tied to the successful completion of re-training measures.

Another focus of attention pursued by the FMF-Germany besides the establishment of standards of performance is the scientific realm. The plan here is to create a central data base in which all data will be stored and evaluated. Data evaluation will be ultimately performed by an independent statistician. A targeted evaluation based on defined focus areas is envisaged.

The General Certification Process for Gynaecologists

Prof. Dr. med. Eberhard Merz

The certification process for gynaecologists falls into three sections:

1. Assessment of prerequisites
2. Successful completion of a course including a theoretical and a practical examination
3. The so-called AUDIT, a review of measurement data in 12-month intervals

ad 1: Admission prerequisites comprise defined knowledge in the field of ultrasound measurement (DEGUM Level II), which means that DEGUM Level I is an precondition to entering the certification process.

ad 2: The certification process requires participation in an FMF-approved training course with defined content and a theoretical examination in the form of a multiple-choice test. Another requirement is the successful completion of a practical examination, whereby the appraisal of results must be based on defined criteria. Candidates must submit five images in order to provide evidence that they are capable of performing correct nuchal translucency measurements. After successful certification, candidates will receive a risk evaluation software which they are required to use for future risk assessment.

ad 3: The AUDIT provides for a submission of measured data and of five ultrasound images to the FMF office in 12-month intervals. If the data stands critical scrutiny, the applicant is granted access to the risk evaluation software for another twelve months. If the reviewed data is sub-optimal, continued access is either denied, or is made contingent upon successful completion of re-training measures.

The General Certification Process for Laboratories

Dr. Helmut Wagner / Dr. Gert Huesgen

In an effort to provide first-trimester screening (11-14 week scan) in Germany with as much diagnostic certainty and reliability as the London-based centre of the Fetal Medicine Foundation under the leadership of Prof. Nicolaides, a group of medical laboratories in Germany have adopted proven practices, namely the implementation of controls as well as the introduction of standardised requirements in regard to biochemical analysis, statistical calculation and case report preparation.

It must be pointed out that this is the first concerted interdisciplinary effort of closely cooperating branches of prenatal and laboratory medicine. This cooperation places them in a position to create more quality and value, to the benefit of women and their children, in terms of individual treatment than any of them could ever provide alone.

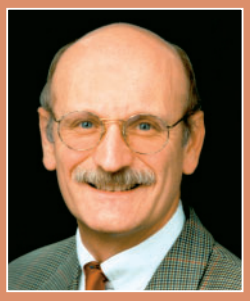
Laboratories have long since contributed their share to quality assurance in prenatal care. The FMF-Germany has now developed a procedure which improves the reliability of diagnostic assessment and which allows to decrease the number of invasive diagnostic interventions formerly triggered by the use of all too often imprecise methods. The laboratory is no longer the more or less sole authoritative judge to determine the quality of the 11-14 scan. A decisive advantage now is the combined performance of, on the one hand, nuchal fold measurement conducted by gynaecologists, and, on the other hand, laboratory-performed biochemical measurement, whereby all measured values are submitted to the same quality assurance principles - including calculations and case report preparation by the laboratory.

For decades, German laboratories have been giving attention to statistical quality monitoring, which divides up into internal and external control processes. The rules for these controls are specified in the guidelines of the German "Bundesärztekammer" (German Medical Association). The statistical, internal quality control process focuses on the precision and correctness of analytic procedures and ensures that individual measured values are reproducible within certain tolerance limits. External quality control, by contrast, involves the monitoring of analytical reliability by so-called interlaboratory trial institutions. The pertinent certificates issued usually have a validity of up to one year. Laboratories which fail to meet these quality assurance targets may not claim payment for services rendered. Additional quality assurance measures are being increasingly implemented in the framework of so far voluntary accreditation procedures.

The 11-14 week scan, which is spread and promoted by the FMF-Germany, provides a completely new quality of information – in the form of an interdisciplinary risk evaluation for the good of pregnant women. The evaluation procedure includes nuchal translucency data as obtained by a certified gynaecologists. The laboratories then carry out the pertinent biochemical analyses and finally establish the overall risk calculation for the respective gynaecologist. This overall calculation is hence based on the combined results of both types of examination. This requires a uniform quality standard! A growing number of laboratories are therefore coming to embrace the professional requirement to safeguard quality assurance throughout the entire procedure by obtaining certification themselves. This certification is voluntary, and is undertaken by laboratories in the interest of comprehensive quality assurance.

The FMF-Germany has established the following regulations:

Laboratories can obtain an FMF certification by signing a "Declaration of Conformity". By doing so, they undertake to use specific FMF-qualified measurement procedures. They also oblige themselves to pass on risk calculation results solely to so-called certified gynaecologists. There is a transitional period until 31st December 2002 during which time gynaecologists who have so far only completed the theoretical part of the examination are allowed to receive risk calculation results. However, this permission is accompanied by the reminder that they should obtain full certification in the shortest possible time. Thanks to the initiative of the FMF-Germany, in which both disciplines (gynaecologists and laboratories) are represented, an increasing number of events will be offered to all gynaecologists willing to obtain certification. From 1st January 2003 on, each of the FMF-certified laboratories will pass on FMF-certified results to fully certified gynaecologists only.



Prof. Dr. med. Eberhard Merz
Director of the Gynaecological Clinic at Northwest Hospital, Frankfurt-on-Main

„The FMF-Germany contributes mainly to an overall improvement of prenatal diagnosis in early pregnancy. Furthermore, the number of invasive interventions can be reduced considerably thanks to the focused and certified method of first-trimester screening."

Dr. med. Dr. rer. Nat. Dipl.-Biochem. Helmut Wagner
Wagner Stibbe Kast Bispink + Partner, Göttingen

„My wish is for the FMF-Germany to be a major contributor to quality assurance in fetal medicine. This involves a turning away from many superfluous examinations, and focusing on quality assurance and control in gynaecological practice for the benefit of the patients."

Dr. med. Gert Huesgen
Laboratory Partnership Leinfelden

„In my view, the concept creates such a high quality standard for all physicians involved that there is little room left for misunderstandings or disadvantages on the patients' side."

Prof. Dr. med. Bernd Eiben
Institute for Clinical Genetics and Cytology North-Rhine, Oberhausen

„We should strive to combine the advantages offered by the decentralised system of prenatal diagnosis in Germany with a quality assurance programme which will represent an optimum system of prenatal care for all parties involved: gynaecologists, laboratory physicians and patients."

Major Messages and Implications: First-Trimester Screening and the FMF-Germany

Prof. Dr. med. Bernd Eiben

There are considerable differences between Germany and other European countries with respect to the state of the art of prenatal diagnosis. In England, for example, prenatal care is based on a rather centralised system, whereas Germany maintains a dense infrastructure of gynaecologists in independent practice and clinics etc. On the one hand, this definitely holds the advantage that we can provide outstanding medical care in terms of area coverage, on the other hand, however, the services offered by all these individual institutions vary substantially in quality. Furthermore, the cooperation of said institutions in the field of quality assurance is fairly weak.

For this reason, the FMF-Germany has been established in the German-speaking realm. It is an association of various interdisciplinary groups of leading gynaecologists, laboratory physicians, human geneticists as well as representatives from industry and research. It aims at ensuring the use of uniform strategies in order to achieve quality improvements in prenatal diagnosis throughout Germany and German-speaking countries; it strives for an ongoing development of prenatal diagnosis under scientific quality control; and it seeks to provide a continuous array of specialised further training measures. Moreover, it envisages an evaluation of future strategies in prenatal diagnosis, besides an establishment of reliable and lasting ties with the press, with self-help groups and hence with pregnant women.

It is one of the association's primary goals to offer first-trimester screening as a standardised, certified method throughout Germany, Austria and Switzerland - subject to the ongoing further training of all participants - with a view to safeguarding effective quality assurance. First-trimester screening is a risk analysis tool for the most common fetal malformations, such as, e.g., cardiac defects or trisomies in the first third of pregnancy, aiming at the lowest possible rate of suspect findings. Participants are certified for one year each, at the end of which they are required to undergo a quality control process. If the result of this review is positive, recertification is granted. This procedure aims at creating a network of certified laboratories, gynaecologists and human geneticists undertaking to perform first-trimester screening under the same conditions and standards. The certification of participants is incumbent on the FMF-Germany.

Priv.-Doz. Dr.Peter Kozlowski
Prenatal Medicine and Genetics, Dusseldorf

„Firstly, diagnostic quality in the first and second trimester of pregnancy will be greatly enhanced. Secondly, I hope that our responsible handling of the data we receive will be one step in the direction of establishing the urgently required malformation register in Germany."

Benefits and Possibilities of First-Trimester Screening Compared with Other Procedures

Priv.-Doz. Dr. Peter Kozlowski

The performance of early screening requires comprehensive and knowledgeable prenatal diagnostic and genetic counselling. Consultation aims at finding out, together with the pregnant woman, to which of the three main groups she belongs.

The first group, which we might call the "invasive group", attaches greatest importance to obtaining a reliable statement with respect to the presence of chromosomal disorders. If these women were expected to put up with a mere likelihood value, they would be downright "undersupplied". However, although many women opt for invasive diagnostic testing, they also undergo early screening. The reason is that they want to gain some inner quiet and bridge the time until the intervention is carried out (usually amniotic fluid sampling in the 15th week of pregnancy) by finding out whether they belong to the "low-risk" or "high-risk" group.

The second group is the so-called non-invasive group. These pregnant women are against invasive diagnostic testing. They usually also reject an induced premature termination of pregnancy, and would even if a disorder were detected. To them it makes no sense to undergo an examination which would only confront them with a decision "for" or "against" invasive diagnostic testing. The third, to my mind biggest, group comprises those women who want to get an idea of their individual risk for chromosomal aberration and other fetal disorders before they will take a decision "for" or "against" invasive diagnostic testing.

Early screening vs. invasive diagnostic testing – strictly speaking, these are diagnostic procedures which defy easy comparison. Early screening tests define risk collectives in regard to the presence of chromosomal disorders and numerous other fetal malformations and diseases. Invasive procedures allow the virtually secure exclusion of detectable chromosomal disorders, whereby amniocentesis furthermore allows the almost complete exclusion of cleft spine (spina bifida). The invasive procedures involve an intervention-related risk of miscarriage of 3 - 10 in 1,000 interventions. The complication rate largely depends on the examiner's experience.

In the western industrialised countries, approximately 15 percent of the mothers of newborn infants are 35 years old or more. In this age group, roughly 35 percent of all children with Down's syndrome are born. If we compare this detection rate of 35 percent, which accounts for a rate of positive findings of 15 percent, with the detection rate of over 90 percent achieved in the FMF study, which accounts for a rate of positive findings of 8 percent, the conclusion will be unambiguous. However, so far no evidence has been furnished to prove that this favourable combination of high detection rate and low positive rate can also be achieved under the condition of a decentralised provision of prenatal care.

Orientation tests geared to assess the likelihood of trisomies and neural tube defects, which have to be carried out between weeks 15 and 18 of pregnancy, have been widely used without sufficient validation and without adequate quality management. This has sometimes resulted in unacceptably high positive rates of between 10 and 20 percent, with sensitivities between 60 and 70 percent. One advantage of the triple test lies in the possibility to screen for neural tube defects, which early screening tests do not offer. The quality and reproducibility of risk assessment through early screening tests depend largely on the quality of the sonographic examination. Soft marker screening, i.e. the evaluation of various body parameters (head shape, neck fold, length of upper arm and upper thigh, hands, renal pelvis, intestine) performed in order to obtain a detailed fetal organ diagnosis has only provided acceptable detection and positive rates when conducted at specialist centres. This procedure is not suitable for widespread use, also because it is performed at an unacceptably late stage of pregnancy. Early screening can detect direct and indirect indications of disturbances in fetal development at a very early stage so that there is usually sufficient time to conduct further diagnostic testing.

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