

Summary and Conclusions

Methods of Early Prenatal Diagnosis

A Systematic Review

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Summary and Conclusions of the SBU Report:

Methods of Early Prenatal Diagnosis

A Systematic Review

December 2007

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Report: Methods of Early Prenatal Diagnosis • Type: Systematic Review

ISBN: 978-91-85413-13-3 • ISSN: 1400-1403

Report no: 182 • Publishing year: 2006

SBU's Conclusions

This report presents the scientific evidence for the methods currently used, or in the process of being adopted, to detect fetal chromosomal and structural abnormalities during early pregnancy. Medical, social, psychological, ethical, health economic, quality assurance and safety aspects of early prenatal diagnosis were analysed.

This summary reviews the questions addressed and the most important conclusions reached in each chapter of the report.

In the first section SBU's main conclusions are presented.

Conclusions

- ❑ A combined test of ultrasound nuchal translucency measurement and maternal serum biochemistry (biochemical screening) in early pregnancy (10–14 gestational weeks), along with maternal age, is the clinically evaluated method of assessing the probability of fetal Down syndrome that gives the best balance between the percentage of detected cases and false-positive results. (Evidence Grade 1)
- ❑ Maternal serum biochemistry with four markers (quadruple test) is the clinically evaluated method of assessing the probability of fetal Down syndrome that in the second trimester gives the best balance between the percentage of detected cases and false-positive results. (Evidence Grade 1)
- ❑ All the methods (nuchal translucency measurement, maternal serum biochemistry in the second trimester and the combined test) for assessing the probability of fetal Down syndrome examined by this report and evaluated in clinical practice gives

a better balance between the percentage of detected cases and false-positive results than maternal age alone. Thus, the use of these methods requires fewer amniocenteses and chorionic villus samplings per detected cases of Down syndrome than maternal age alone. (Evidence Grade 1)

- ❑ Use of the interphase fluorescence in situ hybridization (FISH) test or quantitative fluorescent polymerase chain reaction (QF-PCR) is essentially as accurate as full karyotyping for detecting aneuploidies in chromosomes 13, 18, 21, X and Y. (Evidence Grade 1)
- ❑ Normal results on the rapid FISH test or QF-PCR in prenatal diagnosis leave a residual possibility of fetal chromosomal abnormalities. In approximately 0.9% of all amniocenteses and chorionic villus samplings a full karyotype analysis will detect a chromosomal abnormality missed by the rapid FISH test or QF-PCR. For chromosomal abnormalities of clinical significance, the figure is 0.4%. (Evidence Grade 1)
- ❑ Fewer congenital abnormalities, including heart defects, appear to be detected when a routine ultrasound examination is performed at 12 instead of 18 gestational weeks. That is the case even if the 12-week examination includes nuchal translucency measurement and if increased nuchal translucency or greater probability of chromosomal abnormalities according to nuchal translucency is an indication for a comprehensive fetal anatomy at 18–22 gestational weeks. However, the scientific evidence is insufficient to draw a reliable conclusion in this regard.
- ❑ No detrimental impact of ultrasound exposure during the second trimester has been demonstrated on children's growth, vision or hearing – or their neurological, cognitive or speech

development. No correlation has been demonstrated between prenatal ultrasound exposure and childhood malignancies. (Evidence Grade 1)

- ❑ A meta-analysis of randomized trials have not shown any difference with respect to the frequency of non-right handedness (left handedness or no clear preference) between controls and groups assigned to in utero exposure to ultrasound. Analyses of subpopulations and two Swedish registry studies have found a correlation between such exposure and non-right handedness in boys. However, the scientific evidence is insufficient to draw a reliable conclusion.
- ❑ Invasive tests (amniocentesis and chorionic villus sampling) increase the risk of fetal loss. The best available estimate, which concerns fetal loss after late amniocentesis (15 or more completed gestational weeks), indicates a 1 percentage point increase in the risk. Most of these losses are miscarriages. (Evidence Grade 2)
- ❑ Pregnant women prefer individual to group information. Audio or video information appears to improve their knowledge and understanding somewhat more effectively than letters and brochures. However, most studies reveal inadequacies when it comes to providing information to women prior to prenatal diagnosis. The women are not sufficiently knowledgeable, particularly with respect to the purpose and the potential implications of the results, to make a well-founded decision about whether or not to undergo testing. It is especially difficult for them to understand that nuchal translucency measurement with ultrasound and an evaluation of markers is part of a probability assessment rather than a final diagnosis. (Evidence Grade 1)

- ❑ Most pregnant women want to obtain early information and prefer screening in the first trimester. (Evidence Grade 1)

- ❑ Greater knowledge does not make pregnant women more anxious. The information required to minimize their stress and anxiety levels should be communicated in the same way as that which is provided prior to other medical interventions. Increased anxiety prior to prenatal diagnosis, while waiting for the results or after obtaining notification of detected (or of increased probability of) abnormalities is a natural reaction on the part of the woman and/or her partner. (Evidence Grade 1)

Fact Box 1 Study Quality and Relevance, Evidence Grade.

Study quality and relevance refers to the scientific quality of a particular study and its ability to reliably address a specific question.

Evidence Grade refers to the total scientific evidence for a conclusion, ie, how many high-quality studies support the conclusion.

Evidence Grade 1 – Strong Scientific Evidence

A conclusion assigned Evidence Grade 1 is supported by at least two studies with high quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Evidence Grade 2 – Moderately strong scientific evidence

A conclusion assigned Evidence Grade 2 is supported by at least one study with high quality and relevance, as well as two studies with medium quality and relevance, among the total scientific evidence. If some studies are at variance with the conclusion, the Evidence Grade may be lower.

Evidence Grade 3 – Limited scientific evidence

A conclusion assigned Evidence Grade 3 is supported by at least two studies with medium quality and relevance among the total scientific evidence. If some studies are at variance with the conclusion, the scientific evidence may lower.

Insufficient scientific evidence

If no studies meet the quality and relevance criteria, the scientific evidence is rated as insufficient to draw any conclusions.

Contradictory scientific evidence

If different studies are characterised by equal quality and relevance but generate conflicting results, the scientific evidence is rated as contradictory and no conclusions can be drawn.

SBU's Summary

Introduction

Among the key conclusions of a 1998 SBU report entitled Routine Ultrasound Examination During Pregnancy was that the scientific evidence suggested that fetal examination should be part of the routine ultrasound examination during early pregnancy and that the ethical, organisational and educational implications required further study.

A subsequent conference on early prenatal diagnosis arranged in 2001 by the Federation of Swedish County Councils, the Swedish National Board of Health and Welfare and the Swedish Research Council concluded that, "After comprehensive information has been provided to all pregnant women, prenatal diagnosis should be offered to those who would like to have an examination".

Since the release of the 1998 report, most obstetric departments and clinics have adopted fetal examination as part of their routine ultrasound examination. Meanwhile, technological advances have produced new testing methods. Thus, SBU deemed that it was urgent to update the report, as well as to extend the assessment to other methods – such as maternal serum biochemistry and karyotyping – of early prenatal diagnosis.

The current report is a systematic review of the literature with the intention of examining the scientific evidence for the methods currently used, or about to be adopted, for prenatal diagnosis to detect fetal chromosomal and structural abnormalities. Medical,

social, psychological, ethical, health economic, quality assurance and safety aspects of early prenatal diagnosis have been analysed.

Alongside the review of the literature, a survey was conducted among Sweden's obstetric wards and prenatal health units to determine how early prenatal diagnosis is carried out in clinical practice.

The report closes with an impact assessment of conceivable changes to clinical practice on the basis of the conclusions reached.

During the course of the current project, the Swedish Parliament passed the Act on Genetic Integrity (Swedish Code of Statutes 2006:351). Chapter 4, Section 1 of the act states that, "All pregnant women shall be offered general information concerning prenatal diagnosis. Any woman who is at medically established elevated risk to have a child with abnormalities shall be offered additional information about prenatal genetic diagnosis."

The intention of this report is to provide information and conclusions on the basis of which future healthcare policymakers can determine how early prenatal diagnosis should be carried out in Sweden.

Ethical Aspects

The overall purpose of early prenatal diagnosis is to prevent or minimize suffering. Women are offered an examination during early pregnancy aimed at detecting fetal chromosomal and structural abnormalities. If the results of the examination are normal, it can lessen the anxiety that some women and their partners experience during pregnancy, but they may also have new fears and difficult choices to deal with if abnormalities are detected.

All prenatal diagnosis issues involve complex ethical considerations that affect a number of different people and institutions. There is a great need for a broad-based, community-wide discussion of such matters while maintaining respect for differing opinions

and the awareness that our knowledge remains deficient in many areas. That is particularly true when it comes to the implications of living with various degrees of disability.

The purpose of the report's ethical analysis is to identify and examine the ethical issues related to the methods of prenatal diagnosis under consideration in this report.

During the process of conducting the systematic review, the project group held information sharing sessions with representatives of the Swedish National Council on Medical Ethics (SMER), which performed an overall analysis of ethics and prenatal diagnosis during the same period of time.

Information and invitations to submit viewpoints were sent to concerned groups in the community through all antenatal care units in Sweden and the Swedish Disability Federation.

The Concept of Early Prenatal Diagnosis

In accordance with accepted nomenclature, this report uses the concept of *early prenatal diagnosis* as a generic term. It includes screening offered to pregnant women to assess the probability of fetal chromosomal or structural abnormalities, as well as diagnostic procedures to determine whether such abnormalities are actually present.

Chromosomal abnormalities include changes in the number of whole chromosomes (referred to as aneuploidies or numerical chromosomal abnormalities), as well as loss or changes of parts of chromosomes (structural chromosomal abnormalities). Structural abnormalities occur in the fetal organs with or without concurrent chromosomal abnormalities.

Early prenatal diagnosis refers to tests administered before 22 completed gestational weeks.

Methodology

The systematic review of the literature identified studies that addressed the following questions:

- How accurate are the methods used for early prenatal diagnosis in detecting fetal chromosomal and structural abnormalities?
- What documented risks do the methods pose to the mother or fetus?
- What is known about the cost-effectiveness of the various methods?
- What ethical aspects should be taken into consideration when using the assessed methods of prenatal diagnosis?
- What is known concerning how information provided to the community, pregnant women and their partners concerning prenatal diagnosis should be designed?
- What is known about the psychological aspects of undergoing prenatal diagnosis?
- How are the various methods quality assured?

The report does *not* include the following areas:

- Diagnostic examinations performed in late pregnancy due to suspicion of specific diseases.

- Diagnosis due to specific, uncommon genetic and metabolic diseases on the basis of heredity, conditions in previous children, etc.
- Preimplantation genetic diagnosis.

This report does not attempt to update SBU's 1998 assessment concerning the value of routine ultrasound examinations to establish the expected date of delivery or detect multiple fetuses.

Searches, Reviews and Quality Assessment of the Literature

Literature searches were performed in electronic databases such as Cochrane Library and PubMed/Medline. A search for health economic studies was also conducted in the National Health Service Economic Evaluation Database (NHSEED). Bibliographies were examined and members of the project team followed various areas of current research. Based on predetermined criteria, the identified literature was systematically selected and quality assessed. Randomized trials were reviewed on the basis of the criteria that SBU uses. For studies concerning diagnostic accuracy, the Quality Assessment of Diagnostic Accuracy included in Systematic Reviews (QUADAS) instrument was used and quality was assessed on the basis of predetermined criteria. The criteria for health economic studies were that they should deal with both costs and diagnostic accuracy, be relevant to Swedish conditions and make comparisons with the best alternatives. Quality was assessed on the basis of SBU's checklist for health economic studies. For qualitative studies, a special review instrument developed for previous SBU projects was used. SBU's system for deciding Evidence Grades was also employed.

Result Measures

This report characterizes the diagnostic accuracy of the methods under consideration in terms of sensitivity – along with specificity, percentage of positive test results or percentage of false-positive test results, depending on the measure most often used in the relevant literature.

Below is a description of how the various measures used by the report were calculated. For their general definitions, refer to Appendix 3, Methodological Terms and Concepts, of the report.

Sensitivity is the proportion of all examined fetuses with actual chromosomal or structural abnormalities that had a positive test result.

Specificity is the proportion of all examined fetuses with no actual chromosomal or structural abnormalities that had a negative test result.

The proportion of positive test results is the proportion of all examinations that gave a positive test result.

The proportion of false-positive test results, also known as the false-positive rate (FPR), is the proportion of all examinations in which fetal chromosomal or structural abnormalities were suspected based on the test results but did not actually exist. The FPR and specificity can be derived from each other ($FPR = 1 - \text{specificity}$).

For studies concerning *risks or adverse events*, the report used the following measures: fetal loss (miscarriage, abortion or fetal death), bleeding, premature rupture of the membranes and fetal injury, as well as other complications of pregnancy or adverse effects on the fetus.

For questions involving *ethical, social or psychological* aspects of early prenatal diagnosis, the measures consisted of information, knowledge, decision making, attitudes, anxiety and any impact on parental-fetal bonding.

Results of the Review of the Literature

The results of the literature review are presented as follows: methods of detecting fetal chromosomal abnormalities, methods of detecting fetal structural abnormalities; safety aspects, health economic, ethical, social and psychological aspects and quality assurance.

Methods of Detecting Fetal Chromosomal Abnormalities

The probability of certain fetal chromosomal abnormalities (trisomies) increases with maternal age. Chromosomal abnormalities may be associated with a wide variety of developmental disorders and congenital abnormalities. They also increase the probability of miscarriage or fetal death.

Fetal Down syndrome is the most common chromosomal abnormality of clinical significance for newborns (1 out of 700). The syndrome is due to the presence of all or part of an extra chromosome 21.

Fetal chromosomal abnormalities may be detected by means of amniocentesis or chorionic villus sampling, collectively referred to as invasive prenatal procedures. Up to this point, such procedures have been offered to women over a certain age or for whom other circumstances – such as elevated anxiety levels or previous pregnancies with fetal chromosomal abnormalities – so indicate. Invasive prenatal procedures are associated with increased risk of miscarriage. If maternal age is used as a criterion for performing amniocentesis or chorionic villus sampling, the tests will cause more miscarriages than yield positive results for Down syndrome.

Thus, non-invasive screening methods have been developed in recent years to identify the pregnant women with a greater probability of fetal chromosomal abnormalities. The goal of such methods is to identify as many abnormalities as possible among women who wish to know, while minimizing the number of women who are subjected to invasive diagnosis and the associated risk of miscarriage.

Ultrasound Measurement of Nuchal Translucency as a Screening Method for Down Syndrome

Nuchal translucency measurement involves an ultrasound examination of the fetal nuchal region sometime between 10 and 14 gestational weeks. The method requires high magnification, high-resolution ultrasound equipment and a standardized measurement technique.

CONCLUSIONS

1. The sensitivity of nuchal translucency screening for detecting fetal Down syndrome in an unselected population of pregnant women varies between 43 and 92%. (Evidence Grade 1)
2. Women who are notified of a greater probability of fetal chromosomal abnormalities (positive results) following nuchal translucency screening represent less than 5% of all subjects in most studies of unselected populations. Most of these positive results are false. (Evidence Grade 1)
3. Due to the higher ratio of sensitivity to the proportion of positive results, nuchal translucency screening is more effective than a probability assessment based on maternal age for detecting fetal Down syndrome. (Evidence Grade 1)
4. Although the number of women who undergo invasive diagnosis for fetal chromosomal abnormalities may be less if nuchal translucency screening rather than maternal age is used as the selection criterion, the scientific evidence does not permit any conclusion in this regard.
5. Increased nuchal translucency when the fetal chromosomes are normal or unknown raises the probability of abnormalities, and possibly miscarriage as well. (Evidence Grade 3)

Ultrasound Measurement of Nuchal Translucency as a Screening Method for Other Fetal Chromosomal Abnormalities

CONCLUSION

1. The sensitivity of nuchal translucency screening for detecting fetal chromosomal abnormalities other than Down syndrome in an unselected population varies between 33 and 92%. Women who are notified of an increased probability of abnormalities (positive results) represent less than 5% of all subjects. (Evidence Grade 1)

Fetal Nasal Bone Measurement as a Screening Method for Down Syndrome

Nasal bone ultrasonography can be performed in both the first and second trimester. Absence of a visible fetal nasal bone is regarded as associated with the nasal hypoplasia that may appear in individuals with Down syndrome. The method, which is technically difficult to use, has not been fully assessed or tested in clinical practice.

CONCLUSIONS

1. In unselected populations, sensitivity for detecting Down syndrome varies between 0 and 58%, while positive test results range from 0.5 to 2.7%, during the first trimester. (Evidence Grade 1) Scientific evidence is lacking for the second trimester.
2. In high-risk populations, sensitivity varies between 48 and 69%, while positive test results range from 2.2 to 7.7%, during the first trimester. (Evidence Grade 2)
During the second trimester, sensitivity varies between 28 and 62%, while approximately 3% of the results are positive. (Evidence Grade 1)

Doppler Ultrasonography

Abnormalities in fetal blood flow velocity have been reported in connection with aneuploidy of chromosome 18 or 21, or with increased nuchal translucency, by Doppler ultrasonography of the ductus venosus (a vessel that joins the umbilical vein with the right atrium of the heart) and the tricuspid valve (between the right atrium and right ventricle). As a result, Doppler ultrasonography has been discussed as a screening method for fetal chromosomal abnormalities. Only a handful of studies, all conducted at highly specialized centres, have been conducted so far. The examination is technically difficult to perform and requires highly advanced expertise.

CONCLUSIONS

1. Abnormal Doppler ultrasonography results are associated with increased occurrence of fetal chromosomal abnormalities and/or heart defects. (Evidence Grade 2)
2. Scientific evidence is lacking for the use of Doppler ultrasonography during the first trimester as a screening method for fetal chromosomal abnormalities or heart defects.

Ultrasonographic Soft Markers in the Second Trimester

Obstetric ultrasonography examines the form and structure (morphology) of the fetal organs. The question as to whether ultrasonographic soft markers (morphological abnormalities) may be associated with fetal chromosomal abnormalities has been studied primarily by research projects and has not been subject to sufficient scientific assessment in clinical practice.

CONCLUSIONS

1. Some ultrasonographic soft markers (thickened nuchal fold, echogenic intracardiac focus, echogenic bowel, short humerus

and short femur length) are associated with fetal Down syndrome. Choroid plexus cysts are associated with trisomy 18. (Evidence Grade 3)

2. The occurrence of multiple ultrasonographic soft markers is associated with a greater probability of fetal chromosomal abnormalities. The likelihood increases with each marker. (Evidence Grade 3)
3. There is insufficient scientific evidence for the use of ultrasonographic soft markers as a screening method for fetal chromosomal abnormalities.

Maternal Serum Biochemistry (Biochemical Screening) for Down Syndrome in the Second Trimester

For a number of years, the scientific literature has described a correlation between the level of biochemical markers in the serum of pregnant women and the occurrence of fetal Down syndrome. A number of countries use biochemical markers as a screening method for Down syndrome in the first half of the second trimester (15–21 gestational weeks).

The usual combinations of serum markers are referred to as the:

- double test (alpha-fetoprotein + human chorionic gonadotropin)
- triple test (alpha-fetoprotein + human chorionic gonadotropin + unconjugated estriol)
- quadruple test (alpha-fetoprotein + human chorionic gonadotropin + unconjugated estriol + inhibin-A).

The above tests are combined with maternal age to assess the probability of fetal Down syndrome.

CONCLUSIONS

1. Sensitivity for detection of fetal chromosomal abnormalities by means of biochemical screening increases from 62% for the double test to 70% for the triple test and 79% for the quadruple test, while false-positive results increase from slightly more than 5% for the double test to slightly more than 7% for the quadruple test. (Evidence Grade 1)
2. Combining the quadruple test with maternal age is the current screening strategy for fetal Down syndrome in the second trimester that gives the best balance between detected cases and false-positive results. (Evidence Grade 1)

Combining Ultrasonography and Maternal Serum Biochemistry in the First Trimester

A number of combinations of serum markers and ultrasonography have been studied to assess the probability of fetal chromosomal abnormalities. The markers deemed to ensure the best diagnostic accuracy in the first trimester are pregnancy-associated plasma protein-A and free beta-human chorionic gonadotropin. Maternal serum biochemistry for the above markers, along with maternal age and nuchal translucency measurement, is referred to as the combined test.

CONCLUSIONS

1. In a high-risk population, the combined test in the first trimester has a sensitivity for fetal Down syndrome that varies between 85 and 100% when positive results range from 7 to 10%. In an unselected population, sensitivity varies between 73 and 93% when positive results range from 2 to 7%. (Evidence Grade 1)

2. The combined test in the first trimester has a sensitivity for fetal Down syndrome that is comparable to or higher than the quadruple test in the second trimester. For the same sensitivity, the combined test in the first trimester yields a lower percentage of positive results. (Evidence Grade 1)
3. For the same percentage of positive results, the combined test in the first trimester has higher sensitivity for fetal Down syndrome than nuchal translucency measurement alone. (Evidence Grade 1)
4. Due to insufficient scientific evidence, the question as to whether the combined test would lead to fewer invasive tests for fetal chromosomal abnormalities or fewer newborns with Down syndrome than the maternal age-based screening used by current clinical practice cannot yet be answered.

Genetic Diagnosis

Karyotyping of cultured amniocytes, which has very high diagnostic accuracy (99.4–99.8%) for aneuploidies, is the reference method in invasive prenatal diagnosis for fetal chromosomal abnormalities. Due to the need for cell cultures, the method takes 10–14 days. Newer methods such as the rapid interphase fluorescence in situ hybridization (FISH) test and quantitative fluorescent polymerase chain reaction (QF-PCR) – which do not require cell cultures – yield results in 1–2 days. They can be used to detect the most common aneuploidies but generally not structural chromosomal abnormalities. QF-PCR requires fewer fetal cells and less effort than the FISH test.

CONCLUSIONS

1. The rapid FISH test is essentially as accurate as full karyotyping for detecting aneuploidies in chromosomes 13, 18, 21, x and y. (Evidence Grade 1)
2. QF-PCR is essentially as accurate as full karyotyping for detecting aneuploidies in chromosomes 13, 18, 21, x and y. (Evidence Grade 1)
3. Normal results on the rapid FISH test or QF-PCR during prenatal diagnosis leave a residual possibility of chromosomal abnormalities. In approximately 0.9% of all amniocenteses and chorionic villus samplings, the full karyotyping will detect a chromosomal abnormality missed by the rapid FISH test or QF-PCR. For chromosomal abnormalities of clinical significance, the figure is 0.4%. (Evidence Grade 1)

Methods of Detecting Fetal Structural Abnormalities

Examining fetal anatomy to detect structural abnormalities has been recommended as part of the routine ultrasound examination. Technical advances have enabled earlier detection of such abnormalities.

CONCLUSIONS

1. Sensitivity for detecting fetal structural abnormalities during a routine ultrasound examination at approximately 18 gestational weeks varies among different studies between 19 and 80%, while false-positive results range from 0.06 to 0.5%. (Evidence Grade 2)

2. Sensitivity for detecting fetal structural abnormalities during a routine ultrasound examination at approximately 12 gestational weeks varies among different studies between 9 and 54%, while false-positive results range from 0.04 to 0.32%. (Evidence Grade 3)
3. While sensitivity for detecting fetal structural abnormalities may be less if a routine ultrasound examination is performed at 12 instead of 18 gestational weeks, the scientific evidence does not permit any reliable conclusion in this regard.
4. Although there appears to be a large theoretical probability that even serious and severe structural abnormalities will not be detected by an ultrasound examination during early pregnancy, an examination performed at 12 instead of 18 gestational weeks may possibly lead to earlier detection of serious and fatal abnormalities. The scientific evidence is however insufficient to draw any reliable conclusions.

Methods of Detecting Congenital Heart Defects

Heart defects represent the most common congenital abnormality. Eight out of every 1 000 newborns have heart defects, four of which are severe. The ability of routine ultrasound examinations during pregnancy to detect congenital heart defects has varied substantially in previous studies. Recent technical advances could theoretically improve diagnostic accuracy. Nuchal translucency measurement has also been proposed as a screening method for congenital heart defects. Hence, a separate review of methods of detecting such defects was carried out. An assessment was performed concerning the diagnostic accuracy of the methods, as well as the importance of prenatal diagnosis for treatment and care of the newborn.

CONCLUSIONS

1. Sensitivity for detection of severe congenital heart defects during a routine ultrasound examination at 18–22 gestational weeks varies between 0 and 66%. If the examination is performed at 12–14 gestational weeks, the figures are 0 to 58%. (Evidence Grade 1)
2. Nuchal translucency measurement has low sensitivity for detecting congenital heart defects. (Evidence Grade 1)
3. Fewer congenital heart defects appear to be detected when a routine ultrasound examination is performed at 12 rather than 18–22 gestational weeks. That is the case even if the 12-week examination includes nuchal translucency measurement and increased nuchal translucency is an indication for a comprehensive fetal anatomy examination at 18–22 gestational weeks. However, the scientific evidence does not permit any reliable conclusion in this regard.
4. By allowing for planning of postnatal care and treatment, diagnosis of some congenital heart defects (coarctation of the aorta, left heart obstruction, transposition of the great arteries and hypoplastic left heart syndrome) can improve the newborn's health and most likely reduce neonatal mortality. (Evidence Grade 3)

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a non-ionizing radiation technique. Technical advances, with reduced exposure time, ensure that fetal movements do not impair image quality. As a result, the method is a possible addition to prenatal diagnosis. From the point of view of safety, MRI has been deemed suitable after the first trimester if other non-ionizing techniques are insufficient or if it can be expected to yield data that would otherwise

require exposure to ionizing radiation. This statement is valid for MRI equipment with magnetic field strength up to 1.5 Tesla. The method has not yet been fully assessed.

CONCLUSION

1. MRI may serve as a supplement to ultrasonography for detecting fetal structural abnormalities, primarily in the central nervous system and thorax. (Evidence Grade 3)

Three-Dimensional Ultrasonography

Three-dimensional (3D) ultrasonography is based on the acquisition of two-dimensional images from a tissue volume and subsequent computer reconstruction to a three-dimensional image. Up to this point, 3D ultrasonography has not proven to be a suitable screening method for fetal chromosomal or structural abnormalities. For the time being, the method should be regarded as a supplement to two-dimensional ultrasonography in prenatal diagnosis when there is suspicion or a high probability of fetal structural abnormalities. The scientific evidence is insufficient to assign 3D ultrasonography a meaningful role in prenatal diagnosis.

Safety Aspects

Imaging Methods used for Prenatal Diagnosis

Current diagnostic ultrasound equipment can generate relatively high energy output intensities. The established principle is to perform ultrasonography during pregnancy only if medically indicated, as well as to use short exposure times and the lowest possible energy output intensities. Among the medical indications are routine ultrasound examinations in early pregnancy to establish the expected date of delivery or to detect multiple fetuses.

CONCLUSIONS

1. No detrimental impact of ultrasound exposure during the second trimester has been demonstrated on children's growth, vision or hearing – or neurological, cognitive or speech development. No correlation has been shown between prenatal ultrasound exposure and childhood malignancies. (Evidence Grade 1)
2. A meta-analysis of randomized trials have not shown any difference with respect to the frequency of non-right handedness (left handedness or no clear preference) between controls and groups assigned to in utero exposure to ultrasound. Analyses of subpopulations and two Swedish registry studies have found a correlation between in utero exposure to ultrasound and non-right handedness in boys. However, the scientific evidence is insufficient to draw a reliable conclusion.
3. The scientific evidence for the safety of an ultrasound examination during the first trimester (up to 12 gestational weeks) is insufficient.
4. The scientific evidence for the safety of Doppler ultrasonography during the first trimester is insufficient.
5. The scientific evidence for the safety of 3D ultrasonography is insufficient.
6. An ultrasound contrast agent consists of microbubbles that can interact with the ultrasound beam. There is a theoretical risk of cavitation that damages the fetal tissue. International guidelines recommend great restraint in the use of such agents during pregnancy, but the scientific evidence is insufficient to draw a reliable conclusion.

7. Adverse fetal biological effects have not been shown when using MRI with magnetic field strength up to 1.5 Tesla. The consensus is to refrain from performing MRI scans during the first trimester or using MRI with contrast agents during pregnancy. However, the scientific evidence does not permit any reliable conclusion in this regard.

Methods of Invasive Prenatal Diagnosis

The detection of fetal chromosomal abnormalities currently requires an invasive test (amniocentesis or chorionic villus sampling). Both tests increase the risk of fetal loss (spontaneous miscarriage, abortion or intrauterine death).

CONCLUSIONS

1. The best available estimate, which concerns fetal loss after late amniocentesis (15 or more completed gestational weeks), indicates a 1 percentage point increase in the risk. Most of these losses are miscarriages. (Evidence Grade 2)
2. Late amniocentesis causes fewer fetal losses than chorionic villus sampling through the cervical canal (performed after 10 completed gestational weeks) or early amniocentesis (at 9–14 completed gestational weeks). (Evidence Grade 1)
3. Fetal losses after chorionic villus sampling through the abdominal wall (performed after 10 completed gestational weeks) are of approximately the same magnitude as after late amniocentesis. (Evidence Grade 3)
4. Early amniocentesis increases the risk of talipes (clubfoot) in newborns to 1.6–1.8%, as opposed to the 0.1% reported after late amniocentesis and 0.2 after chorionic villus sampling through the abdominal wall. (Evidence Grade 1)

Health Economic Aspects

Most relevant studies were model analyses based on data from clinical trials or cost accounting systems. This report assessed such studies for quality but did not rate them for quality and relevance. As a result, the conclusions were not graded for evidence.

CONCLUSIONS

1. A combined test of ultrasound nuchal translucency measurement and maternal serum biochemistry in the first trimester is more cost-effective than maternal serum biochemistry (the triple test) in the second trimester.
2. A routine ultrasound examination in the second trimester is a cost-effective method of detecting fetal structural abnormalities.

Ethical, Social and Psychological Aspects

The generally accepted ethical principles of beneficence, non-maleficence, respecting the patient's autonomy and justice can all be applied to prenatal diagnosis issues. Following a preliminary bill entitled "Genetics, Integrity and Ethics" (Swedish Government Official Reports 2004:20), Swedish Government Bill 2005/06:64 stressed the ethical principles of respect for the patient's autonomy, as well as the importance of informed consent.

The development of new prenatal diagnosis methods – including more advanced ultrasound techniques, maternal serum biochemistry and simplified karyotyping – highlights the urgency of ethical analysis based on the above principles. Thus, the systematic review of the literature focused on information, knowledge, decision making and attitudes, anxiety and any impact on parental-fetal bonding based on the prenatal diagnosis methods examined by this report.

Systematic reviews of the literature, original papers and Swedish academic theses serve as the basis for the conclusions below.

Information, Knowledge, Decision Making and Attitudes

In promoting informed, voluntary decisions by a pregnant woman and her partner, informational issues are of utmost importance – particularly when it comes to autonomy and justice. Various methods of communicating knowledge, assessing how women and their partners experience the information that they receive, and their ability to proceed from it in order to make informed decisions have been analysed.

Beyond the Swedish studies that were identified, most of the published studies were conducted in the United Kingdom, United States, Australia and a few other Western European countries. Remarkably enough, no Swedish studies have specifically examined these issues on the basis of ethnic or social considerations.

CONCLUSIONS

1. Many models of information on prenatal diagnosis have been tried. Pregnant women prefer individual to group information. Audio or video information appears to improve their knowledge and understanding somewhat more effectively than letters and brochures. However, most studies reveal inadequacies when it comes to providing information to women prior to prenatal diagnosis. The women are not sufficiently knowledgeable, particularly with respect to the purpose and potential implications of the results, to make a well-founded decision about whether or not to undergo testing. It is especially difficult for them to understand that nuchal translucency measurement with ultrasound and an evaluation of markers provide a probability assessment rather than a definitive diagnosis. (Evidence Grade 1)
2. Most pregnant women want screening for Down syndrome before an invasive test is performed and feel that it gives them more reliable information with which to make a well-founded

decision. Most of them want to obtain the answer early in pregnancy and prefer screening in the first trimester. (Evidence Grade 1)

3. The fact that pregnant women and their partners see prenatal diagnosis as a means of ensuring that the baby is normal, while the medical profession is focused on detecting fetal abnormalities, can make it more difficult to provide proper information. (Evidence Grade 3)

Psychological Aspects

The primary ethical principles involved in the question of what impact prenatal diagnosis has on a pregnant woman and her partner in terms of anxiety levels, well-being and parental-fetal bonding are the imperatives to do good and prevent suffering.

CONCLUSIONS

1. Greater knowledge does not make pregnant women more anxious. The information required to minimize their stress and anxiety levels should be communicated in the same way as before other medical interventions. Increased anxiety prior to prenatal diagnosis, while waiting for the results or after obtaining notification of detected (or increased probability of) abnormalities is a natural reaction on the part of the pregnant woman or her partner. (Evidence Grade 1)
2. Early prenatal diagnosis does not appear to affect maternal-fetal bonding. While waiting for the results of an invasive test, some women may be in temporary denial about their pregnancy. However, the scientific evidence is insufficient to draw a reliable conclusion in this regard.

Quality Assurance

According to Chapter 4, Section 2 of the Swedish National Board of Health and Welfare's Management System for Quality and Patient Safety in Health and Medical Care (SOSFS 2005:12), the system must ensure that there are routines for testing, adopting, applying, monitoring and modifying new diagnostic, care and treatment methods.

Quality assurance is of fundamental importance for all prenatal diagnosis routines, for the individual methods as well as for the overall organisation. Because there is a lack of scientific support for evidence-based conclusions that proceed from SBU's criteria, this report discusses quality assurance from the standpoint of patient safety, performance, training, resource utilisation, etc. The chapter is based on a summary of the knowledge and experience found in the available literature, as well as national and international guidelines and recommendations.

2004 Survey of Clinical Practice

In cooperation with the Swedish Society of Obstetrics and Gynecology (SFOG), SBU conducted a survey to determine how clinical practice in Sweden had changed since its 1998 Routine Ultrasound Examination during Pregnancy report and the 2001 national conference on early prenatal diagnosis. Focusing on the situation in 2004, the survey covered the following areas:

- Information provided to pregnant women and their partners about prenatal diagnosis
- Organisation of routine ultrasound examinations
- Documentation, quality control and training for routine ultrasound examinations
- Routines for invasive prenatal diagnosis.

Information about maternal serum biochemistry was obtained from Karolinska University Hospital in Stockholm and Statens Serum Institut in Copenhagen.

A questionnaire was sent to all obstetric departments and clinics, as well as private providers of antenatal health care, in Sweden. All the questionnaires were filled out and returned. The results, the most important of which are summarized below, include the responses of 54 units that provide obstetric and/or antenatal care.

1. With rare exceptions, all units informed pregnant women that prenatal diagnosis is voluntary. The time set aside to provide the information varied, but ranged from 5 to 10 minutes for approximately half of the units.
2. Most of the units performed a routine ultrasound examination at 15–20 gestational weeks. Almost 90% of the units included an evaluation of fetal anatomy. Approximately 80% of the units followed SFOG's Quality Assurance of Routine Ultrasound Examinations or another quality assurance system.
3. No unit offered nuchal translucency measurement to all pregnant women, but 13 offered it either to selected populations or upon request. A total of 8 000–9 000 nuchal translucency tests were performed in Sweden during 2004.
4. The number of ultrasound examinations varied considerably among different examiners. A total of 52 examiners at 22 units performed fewer than 200 routine ultrasound examinations in 2004.
5. All units used full karyotyping for genetic diagnosis in 2004. Most of them employed full karyotyping only, while the others

combined it with either the rapid FISH test or QF-PCR. The percentage of miscarriages after an invasive test was generally in line with that reported by the literature but was often based on a very small number of cases.

6. Maternal serum biochemistry, almost always the triple test, was performed in just under 900 cases in 2004.

Impact Assessment of Conceivable Changes to Clinical Practice

Clinical practice varies considerably among the care units that provide prenatal diagnosis in Sweden. Changing routines in accordance with the conclusions drawn from the review of the literature would require substantial additional resources, including investment in upgraded equipment and facilities, staff training and the time needed to supply pregnant women and their partners with proper information. The inclusion of an ultrasound examination in both the first and second trimester would boost annual costs by an estimated 56%, or more than 100 million Swedish crowns. The cost increase would be less if the introduction of first-trimester ultrasound examinations reduced the number of routine examinations in the second trimester, estimated to 8.6 million Swedish crowns (4.6%) if second trimester ultrasound examinations were wholly replaced by first-trimester examinations.

The additional cost should be weighed against the advantages of more qualified information to the pregnant women and their partners and greater accuracy in detecting as many fetal chromosomal abnormalities as possible among women who wish to find out, while minimizing the number of women who are offered an invasive test due to the increased probability of such abnormalities and thereby avoiding induced miscarriages.

Unanswered Questions

The clinical value of nasal bone ultrasonography, ultrasonographic soft markers, Doppler ultrasonography, 3D ultrasonography or MRI as screening or prenatal diagnosis methods in the first or second trimester remains unclear.

The clinical effectiveness of using the integrated or individual risk-orientated two-stage first-trimester screening (contingent screening) models for detecting Down syndrome is unknown.

Scientific evidence is lacking to determine whether there are risks associated with using two-dimensional or Doppler ultrasonography in the first trimester, or 3D ultrasonography in the first or second trimester.

There is a lack of scientific evidence to determine whether there may be a cause-effect relationship between in utero ultrasound exposure and non-right handedness in boys.

There is a lack of knowledge concerning which models are most suitable for supplying pregnant women and their partners with suitable information, or how it should be formulated to satisfy the needs of particular ethnic and cultural groups.

Evidence-based knowledge is lacking with regard to the cost-effectiveness for quality assurance models.

There is a lack of health economic evaluations, based on Swedish conditions, of various screening strategies for fetal chromosomal abnormalities.

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SBU Evaluates Health Care Technology

Below is a brief summary of the mission assigned to SBU by the Swedish Government:

- SBU shall assess healthcare methods by systematically and critically reviewing the underlying scientific evidence.
- SBU shall assess new methods as well as those that are already part of established clinical practice.
- SBU's assessments shall include medical, ethical, social and economic aspects, as well as a description of the potential impact of disseminating the assessed health technologies in clinical practice.
- SBU shall compile, present and disseminate its assessment results such that all parties concerned have the opportunity to take part of them.
- SBU shall conduct informational and educational efforts to promote the application of its assessments to the rational use of available resources in clinical practice, including dental care.
- SBU shall contribute to the development of international co-operation in the field of health technology assessment and serve as a national knowledge centre for the assessment of health technologies.

Methods of Early Prenatal Diagnosis

The SBU report is based on a systematic and critical review of the scientific literature. It is one of a series of scientific reports published by SBU (The Swedish Council on Technology Assessment in Health Care).

The Summary and Conclusions of the report, presented in this booklet, have been approved by the SBU Board of Directors and the Scientific Advisory Committee.