Executive summary

Health Council of the Netherlands. Prenatal Screening: Down's syndrome, neural tube defects, routine-ultrasonography. The Hague: Health Council of the Netherlands, 2001; publication no. 2001/11

The present advisory report, produced by a Health Council committee, is a response to questions which the Minister of Health, Welfare and Sport has put to the Council with regard to methodological, psychological, ethical and legal aspects of various forms of antenatal screening for Down's syndrome and neural tube defects and of routine ultrasound examination during pregnancy.

Antenatal screening for Down's syndrome and neural tube defects

In the Netherlands antenatal screening for Down's syndrome and other chromosomal abnormalities has been offered to pregnant women aged 36 and over since the 1970s (up until 1985 the threshold was 38). The woman can choose between an amniocentesis (from 15 weeks of pregnancy) and chorionic villus sampling (from 10 weeks). Both methods involve an invasive procedure, with a small risk of miscarriage (about one per cent). Because of that risk — but also for practical and financial reasons — the screening is not offered to all pregnant women, but only to those who, on account of their age, are at increased risk of having a child with a chromosomal abnormality. In young women that risk is relatively small, but above the age of 30 there is a rapid and progressive increase. The threshold that has been adopted (36 years) is relatively arbitrary.

Neural tube defects (anencephaly, spina bifida) can be detected by ultrasound scanning or amniocentesis (not by chorionic villus sampling), but the risk of having a child with such a defect is not dependent on the age of the woman. The

risk-assessment test that is available in order to screen for these abnormalities involves determining the concentration of alpha-fetoprotein (AFP) in maternal serum. The use of such a test (known as the MSAFP: maternal serum AFP) has the same function as the maternal age criterion in the above methods of Down's syndrome screening: i.e. it serves to identify a group of women who qualify for ultrasound scanning or amniocentesis because they are at increased risk of having a child with a neural tube defect. MSAFP screening for neural tube defects has been introduced in various countries since the late 1970s, but not in the Netherlands.

In the mid-1980s it emerged that the AFP concentration in maternal serum is also a suitable indicator for the risk of Down's syndrome. Since that time, many programmes have been offered abroad that consist of combined screening for Down's syndrome and neural tube defects. For the purposes of Down's syndrome screening, the test has been supplemented with two other markers — human chorionic gonadotrophin (hCG) and unconjugated oestriol (uE_3) — giving rise to the so-called "triple test". This can be used from 15 weeks of pregnancy (or 14 weeks if screening is for Down's syndrome only). If the test result is abnormal, the woman is offered ultrasound scanning (for neural tube defects only) or amniocentesis.

For Down's syndrome screening, alternative risk-assessment tests have recently been proposed which are either claimed to offer better test characteristics than the triple test or else have the potential advantage that they can be used in the first trimester of the pregnancy. These involve:

- the addition of a fourth marker to the triple test (resulting in a "quadruple test")
- a serum test which can be used from 8 weeks and is based on two or more markers
- ultrasound risk assessment based on the measurement of a subcutaneous accumulation of fluid (nuchal translucency, NT), visible between 11 and 14 weeks, behind the neck of the foetus (a correlation has been discovered between the extent of this fluid accumulation and the risk of Down's syndrome)
- a combination of the two tests mentioned above
- a combination of risk-assessment tests in the first and second trimesters (the "integrated test").

The scientific data offered in support of these alternative risk-assessment tests is not yet as strong in every respect as for the triple test. One potentially attractive, but as yet theoretical, approach is the prospect of screening for Down's syndrome by examining foetal cells present in maternal blood.

The Committee has had a cost-effectiveness analysis conducted which compares various strategies for antenatal Down's syndrome screening. A comparison of screening based on the triple test (offered to all pregnant women) with existing maternal

age-based screening programmes (offering amniocentesis or chorionic villus sampling to pregnant women aged 36 and over) shows that:

- the ratio between the number of Down's syndrome pregnancies detected and the number of miscarriages caused by the procedure (the "detection/miscarriage" ratio) is considerably more favourable for triple test-based screening than for the existing policy of maternal age-based screening
- the costs per case of Down's syndrome detected ("cost/detection" ratio) for both approaches are virtually identical.

Also included in the analysis are the newly developed tests and test combinations mentioned above, regardless of the amount of supporting scientific data. Comparisons between the different methods show that there is little difference in cost-effectiveness between strategies based on the serum tests that can be used in the first or second trimester. In that respect there is also scarcely any difference between those strategies and screening based on NT measurement. The combination strategy of NT measurement and serum screening in the first trimester (the "double test") does appear to correlate with a markedly better detection/miscarriage ratio than the best approach in the second trimester (the quadruple test). Only the "integrated test" has an even better detection/miscarriage ratio, but this approach results in higher costs per detected case of Down's syndrome.

The risk-assessment tests proposed for Down's syndrome screening in the first trimester cannot be used to screen for neural tube defects. Risk-assessment screening for neural tube defects is only possible by means of MSAFP determination in the second trimester of the pregnancy (possibly as part of a triple or quadruple test). Ultrasound screening between 18 and 21 weeks has been proposed as an alternative approach, the advantage being that a direct answer is obtained regarding the absence or presence of a neural tube defect. The Committee suspects that the sensitivity of this approach (for spina bifida) measures up to that of screening based on the MSAFP test. It remains to be seen whether or not this is the case in practice. With ultrasound screening, the costs will most probably prove to be higher. According to the Committee, it is appropriate to screen for neural tube defects, considering the incidence of these abnormalities and the fact that the majority of pregnant women request a termination if a neural tube defect is detected in the foetus.

Ultrasound examination in pregnancy

The purpose of the ultrasound scan as a diagnostic instrument is to monitor the course of the pregnancy with a view to optimising obstetric care. A distinction is made between a "dating scan" (known in the Netherlands as the *termijnecho*), which is

performed in the first trimester and is primarily intended to determine the gestational age and identify a possible multiple pregnancy, and an "ultrasound anomaly scan" (*standaardecho*), performed later in the pregnancy, which is, in part, aimed at ruling out (or else identifying) structural abnormalities. The optimal period for the latter scan is between 18 and 21 weeks.

The scientific literature does not provide sufficient hard evidence to support the use of ultrasound screening for structural abnormalities other than neural tube defects. Nor, it should be noted, has routine ultrasonography been shown to have any conclusive effect on actual clinical outcome measures. Given the limited nature of the research so far conducted in this area, however, such an effect cannot be ruled out. There are indications suggesting that routine ultrasonography can favourably influence the ultimate prognosis of certain conditions of relevance to obstetric management.

Psychology

In a large proportion of the target group there is a positive attitude towards antenatal screening for Down's syndrome or neural tube defects. At the same time, there appears to be a preference for non-invasive tests and for testing to take place as early in the pregnancy as possible. The principal reason for wishing to undergo screening is the need for reassurance. Little research has been done as yet into the reasons why pregnant women do not respond to an offer of screening. There is no evidence that the complexity of the information to be processed in the context of risk-assessment screening precludes well considered decision making. However, it is clear that the information and counselling provided in relation to this type of screening have to meet high quality standards. In this respect, further research is needed into the dynamics of decision making throughout the entire screening process.

There is no evidence that the psychological effects of an abnormal result from a risk-assessment screening test in the second trimester are so serious as to make it unacceptable to offer such a test. Further research is needed into certain aspects — including the consequences of a false-negative test result — with an eye to the quality of counselling and support. Scarcely any research has been conducted to date into the psychological consequences of risk-assessment screening in the first trimester (serum test, NT measurement or a combination).

Great interest has been shown in routine ultrasonography during pregnancy. Providing it does not reveal any abnormal findings, ultrasonography reduces feelings of anxiety and has a positive effect on the way the pregnancy is perceived. As yet, little research has been conducted into the consequences of abnormal outcomes whose clinical significance is either unclear or uncertain, or into decision-making in such situations.

Ethics

In the Committee's opinion, evaluation of antenatal screening should be undertaken against the background of the general evaluation framework that was formulated in an earlier Health Council advisory report (GR94) with reference to internationally applied criteria. Based on this framework, the Committee believes that antenatal screening for conditions such as Down's syndrome or neural tube defects can be morally justifiable if the purpose of this screening is either to enable pregnant women and their partners to have the pregnancy terminated in the event of an abnormal result, or to prepare them for the birth of a child that may possibly be severely handicapped.

When weighing up the advantages and disadvantages of the screening service for those involved, the scales will, however, need to tip clearly in favour of the advantages. According to the Committee, a fundamental difference between the prospect of offering the triple test to all pregnant women and the accepted practice of maternal age-based screening for Down's syndrome lies in the fact that a screening programme based on the triple test would require considerably fewer invasive procedures (amniocentesis and chorionic villus sampling) in order to be able to detect more Down's syndrome pregnancies. This means a concomitant reduction both in the number of miscarriages caused by those procedures and in the associated psychological stress, while a far larger group — i.e. (in principle) all pregnant women — can take advantage of the screening. In the opinion of the Committee, this outweighs the specific disadvantages associated with the fact that the triple test is based on risk assessment. It is not yet possible to make a definitive evaluation of the advantages and disadvantages of risk-assessment screening in the first trimester.

The routine nature and the complexity of risk-assessment screening make the task of offering and performing the screening in such a way that those involved are genuinely able to make a well-considered decision with regard to the various choices that arise during the overall screening process all the more challenging. To avoid the risk of information overload, the Committee advocates a phased approach of informed consent.

In order to assess the acceptability of prenatal screening, the possible consequences for individuals outside the target group are also of relevance, as is its impact on society as a whole. Concerns that the introduction of risk-assessment screening for all pregnant women may contribute to a climate in which societal acceptance of the (mentally) handicapped will come under even greater pressure need to be taken seriously. If participation in screening and termination of pregnancy in the event of an unexpectedly abnormal screening result are not expressly presented as choices, then the implicit message will be that anyone who makes a different choice is acting injudiciously. From there it is but a short step to the notion that pregnant women who "risk" having a sick or

handicapped child — or who do not wish to have an affected pregnancy terminated — are placing an unnecessary burden on society. It is therefore vital that we should not merely pay lip service to the goal that was mentioned earlier (i.e. providing choices), but that it should actually be manifested in the way the screening is delivered in practice. Also important in this connection is the broader context as regards society as a whole. If pregnant women or couples who are expecting a child with a severe handicap are to be offered a genuine choice between termination and allowing a pregnancy to continue to term, then facilities and conditions need to be guaranteed within society for the care, support and integration of people with a handicap. The promotion and monitoring of this situation is an important responsibility of government.

Legal implications

Screening is delivered on the basis of an unsolicited offer made by a care provider or medical institution. This has health care-law implications, both in relation to the justification for that offer and in terms of the legal position of (prospective) users of the service. An important precept is the fact that screening cannot be predicated on certain assumptions that are widely accepted in the field of curative health care. This means, *inter alia*, that explicit informed consent is always required in connection with screening.

The Population Screening Act (WBO) sets out to provide protection against potentially hazardous forms of population screening. Under this Act, a permit is required in order to screen populations for serious diseases or abnormalities for which treatment or prevention is not possible. Since Parliament has stated that termination of pregnancy must not be regarded as a form of prevention, a permit is required in the case of antenatal screening for Down's syndrome and neural tube defects. The WBO also provides (in section 7, subsection 3) that a permit will only be issued "if special circumstances provide justifying grounds". If this provision were to be strictly interpreted, it would virtually be tantamount to an outright ban on antenatal screening for such conditions as Down's syndrome or neural tube defects. Since such a stance is difficult to justify given the aim of the WBO, the Health Council has tended to argue that the provision in question should be interpreted as leaving scope (in principle) for this form of screening - an interpretation with which the Committee concurs.

Conclusions and recommendations

Providing the conditions laid down in this advisory report — including those regarding informed consent — can be satisfied in practice, then risk-assessment screening for Down's syndrome would be such a superior alternative to the existing practice of

maternal age-based screening that there should be no reason to delay its introduction any longer. Subject to the same conditions, the Committee also regards the introduction of screening for neural tube defects as a desirable step.

Introduction of risk-assessment screening

It would be quite possible for risk-assessment screening to be introduced in the near future as a healthcare service if it were to be based on the triple test – this being both the most tried and tested, and organisationally the least ambitious, approach. The test can then be offered as a combined screening programme for Down's syndrome and neural tube defects. The professional groups involved must assume collective responsibility for delivering the screening in accordance with the requisite guidelines (which need to be fleshed out), for the necessary staff education and training, for the recording of results and other relevant aspects of the screening process, and for the evaluation of screening services. The Committee views the extra demands that will be made on the time of the obstetric caregivers in primary and secondary care as a significant problem. The existing antenatal diagnostic centres are well equipped to handle follow-up screening and to provide the necessary support – including any decision that might need to be taken on whether or not the pregnancy is to be terminated.

Although the most cost-effective strategy would be to limit the offer of risk-assessment screening to the group that already qualifies for Down's syndrome screening, the Committee does not regard this as the approach that should be adopted. The overwhelming majority of children with Down's syndrome are born to younger mothers. They too should be allowed to benefit from the opportunity to have their individual risk of such a pregnancy outcome assessed by means of screening. Pregnant women aged 36 and over may be taken unawares if the existing range of services is replaced by risk-assessment screening. The Committee feels that this is something that needs to be taken into consideration and proposes that pregnant women of 36 and over should, at least for the time being, be given the opportunity to have an amniocentesis or chorionic villus sampling without prior testing if they express a wish to this effect during the counselling. The Committee anticipates that the demand for this opportunity to opt for an invasive procedure from the outset will gradually decline.

In terms of organization, one might consider regional institutions, which may act as legal entities in the application for the required WBO permits. Before applying for the WBO permit it is necessary to undertake a pre-implementation strategy, which is designed to furnish guarantees with regard to the quality of performance:

- The professional groups involved need to draw up guidelines for the various components and aspects of the screening programme (including the counselling).

- In order to guarantee the quality of the counselling, staff education and training programmes are required for all of the obstetric caregivers involved in the screening programme. In addition, one could train specialist (obstetric) counsellors. Specific training also needs to be provided in order to inform general practitioners not actively involved in obstetrics of the purpose, design and organisation of the screening.
- The participating laboratories must work in accordance with an accredited quality assurance system that is based on international standards (e.g. ISO 15189). The laboratory needs to perform sufficient assays to accrue statistically reliable median values. Depending on the number of participants, there might be between five and eight laboratories, each of them conducting 10 - 20,000 assays per year.
- Part of the pre-implementation strategy should consist in reviewing the phased approach based on informed consent that has been proposed in this advisory report.

Standard offer and trial population screening programmes

In order to avoid the screening programme being shackled for a prolonged period to a situation that is conspicuously in flux, the Committee advocates that introduction should be based on the triple test coupled with the establishment of a structure that encourages research into newly emerging screening possibilities. The Committee feels that such research is best fostered by entrusting the initiative to the providers in each individual region. In regions where such initiatives are not developed — or at least not at this point in time — one would need to offer the triple test for screening for both Down's syndrome and neural tube defects.

The trial population screening programmes referred to here also require a permit under the WBO act. The research must be designed in such a way that, according to the result, decisions can be taken with regard to any adjustment that might need to be made to the screening service that is being offered. In principle, this means that every practice in the region concerned must join in with the research. Moreover, trial projects must be required to offer a coherent screening programme for Down's syndrome and neural tube defects. This means that in regions where screening for Down's syndrome is offered (in a research context) in the first trimester, separate screening for neural tube defects must also be provided. The Committee recommends that this be accomplished by offering all pregnant women a routine ultrasound scan between 18 and 21 weeks (also in the form of a trial population screening programme). For pregnant women who do not wish to take part in research into potential new screening methods, the standard screening test (the triple test) must be available.

For research into ultrasonography-based screening, separate guarantees need to be established in addition to those pertaining to the quality aspects already mentioned. The

Committee recommends that this research be carried out in regional "transmural" ultrasound screening centres. These centres are to be established in collaboration with existing antenatal diagnostic centres, whose experience and expertise is invaluable. For screening that is partly based on NT measurement, supplementary training requirements are to be made for the gynaecologists and (other) sonographers who perform the screening.

Registration and evaluation

Prenatal screening for Down's syndrome and neural tube defects needs to be subject to ongoing evaluation (i.e. monitoring), which must be conducted at a national level. For this purpose a central body will need to be appointed or created, whose task will include making proposals, based on its findings, for optimising screening programmes or for research to this end. The Committee proposes that this function should be entrusted to the Health Insurance Council (CvZ), in which case it will be possible to link up with the existing Committee on Pre- and Postnatal Screening (CPPS).

The ongoing evaluation referred to demands that the results of all regional programmes be recorded at a national level - giving due consideration, of course, to the relevant statutory requirements. One possibility might be a link-up with the national obstetrics and neonatology registrations (LVR/LNR). A further essential step is the establishment of a separate, nationwide register of congenital abnormalities. The responsibility for financing the evaluation and registration systems, which are indispensable components of the screening as a whole, lies with government and the insurers.

In making its evaluation, this central body should also take into account the results of regional trial population screening programmes. If the outcome of the evaluation is positive, an application can be made for a WBO permit authorising the applicant to offer the screening programme in question as a healthcare service (either alongside or instead of the triple test).

Routine-ultrasonography

As long as the triple test serves as the standard approach when screening for Down's syndrome and neural tube defects, there is no reason (based on the scientific data presented in this advisory report) for routine ultrasonography to be offered during pregnancy. Nevertheless, the Committee feels that policy needs to be adjusted in this regard to pave the way for a routine ultrasound at the outset of the obstetric care programme (a "dating scan"). The Committee points to the practice of uncoordinated routine ultrasonography that currently prevails in the Netherlands (90% of all pregnant

women have at least one scan). For this practice, the development of guidelines and evaluation can be expected to yield benefits in terms of quality. Of further relevance is that the proposed strategy for introducing screening for Down's syndrome and neural tube defects will admittedly lead to a situation in which pregnant women in regions offering trial population screening programmes will, in some cases, be offered two routine scans. If the present policy with regard to routine ultrasonography is continued, a major discrepancy would arise in comparison with regions that are, for the time being, only performing the triple test.

The professional groups must be asked to draw up guidelines for the performance of a routine ultrasound scan (the "dating scan") at the outset of the obstetric care programme, including a strict delineation of its obstetric goal. It would also be desirable to include this in the above evaluation and registration procedure.