EVALUATION OF SCREENING STRATEGIES FOR DOWN'S SYNDROME

Public Health Guideline

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**SUMMARY**

Trisomy 21 or Down’s syndrome is the most frequently occurring chromosomal abnormality. It is caused by the presence of a supernumerary chromosome 21 and may result in multiple anatomical malformations, a specific phenotype and more or less severe mental retardation. The prevalence of trisomy 21 increases with maternal age (total prevalence of 7/10,000 pregnancies in women aged 20-24 years versus 59/10,000 pregnancies in women aged 35 years or more, according to data from 23 European Eurocat registers in 2002).

Antenatal diagnosis to identify Down's syndrome foetuses, based on karyotype analysis of a specimen of foetal cells, was developed about thirty years ago. However, because of the risks associated with techniques used to sample foetal cells (primarily foetal loss), the small number of cytogenetic laboratories and the cost of the examinations, antenatal diagnosis of Down's syndrome is not systematically proposed to all expectant mothers in any country whereas antenatal screening has been well developed.

The purpose of antenatal screening is to provide women and couples who so wish with the most objective information about the risk of foetal trisomy 21 in the current pregnancy. It includes all the methods used to distinguish women at high-risk, who will be proposed a diagnostic procedure, from women at low risk. A result higher than the selected risk threshold does not mean that the foetus is affected but opens the possibility for reimbursement by National Health Insurance of diagnosis by foetal karyotyping using foetal cells collected by amniocentesis, choriocentesis or cordocentesis. This antenatal screening is particular as it means that the pregnant woman must choose between termination or continuation of pregnancy if the diagnosis is positive. The nature of this alternative and the moral suffering and deontological difficulties surrounding this decision mean that ethical considerations are of major importance during antenatal screening for Down's syndrome. Under these conditions, all possible solutions for the management and preparation for birth of a Down's syndrome child must systematically be considered and proposed.

Since the middle of the 1970s, developed countries have set up various policies to provide access to antenatal diagnosis of Down's syndrome. Initially based on maternal age, these policies changed after the discovery of different markers in maternal blood and the identification of ultrasound signs allowing the development of new more effective screening strategies. Since 1997, antenatal screening of Down's syndrome forms part of the French regulatory framework. All pregnant women must systematically be offered screening of at least two serum markers (hCG or the free β-hCG sub-unit and AFP or estriol). This may only be achieved between the 15th and 18th weeks of gestation and only by authorised laboratories. When the estimated risk of foetal trisomy is above a risk cut-off value of 1/250 at the time of screening, the woman is offered amniocentesis for foetal karyotyping (reimbursed by National Health Insurance). Amniocentesis and foetal karyotyping are also reimbursed in women aged 38 years or more, and in the case of an ultrasound abnormality.

Down's syndrome screening practices have gradually diversified beyond the framework defined by the regulations. In parallel with second trimester serum screening, first-trimester ultrasound measurement of nuchal translucency has progressively become more widely used for screening for foetal aneuploidy including Down's syndrome. The coexistence of these screening strategies has lead in France to an amniocentesis rate of about 11%. However these invasive diagnostic investigations may cause foetal loss (the amniocentesis-related foetal loss rate is estimated to be between 0.5 and 1%) generating anxiety for the women who use them.

In parallel with the progress in practices, new Down's syndrome screening strategies have been developed, studied and disseminated since the middle of the 1990s. The main objective of these
new approaches has been to improve the performance of antenatal Down's syndrome screening by obtaining higher detection rates and lower false positive rates in order to reduce the number of invasive surgical procedures. Two main new approaches have been studied in particular:

- Earlier antenatal screening for Down's syndrome from the first trimester of pregnancy by screening for two new serum markers (PAPP-A and β-hCG free fraction) and ultrasound measurement of nuchal translucency;
- Combination of different first and second-trimester screening markers using integrated strategies to obtain a single risk cut-off from all the available information.

This progress makes the choice offered to women and couples more complex and it is necessary to clarify the current situation so that conditions for obtaining free and informed consent to Down's syndrome screening are maintained. The General Directorate of Health and more recently the Collectif interassociatif autour de la naissance (French Inter-Association Taskforce for Childbirth) and the French National Board of gynaecologists and obstetricians therefore asked the HAS to evaluate the role of new first-trimester screening strategies for Down's syndrome.

The main practitioners targeted by this public health guideline are general practitioners, gynaecologist-obstetricians, medical gynaecologists, midwives, cytogeneticists, clinical laboratory specialists approved for the screening of Down's syndrome, sonographers conducting obstetric ultrasound scans and all practitioners working in antenatal diagnosis centres (CPDPN).

I. STUDY METHOD

The HAS working method is based on a systematic and critical review of the literature referenced in bibliographical databases (Medline, Embase, Pascal, Cochrane Library, National Guideline Clearinghouse, public health data bank) or obtained from other sources (Internet: search engines, selected bibliography of articles and documents). Documents were searched on all topics concerning screening for Down's syndrome and its public health dimensions (performance, effectiveness, acceptability etc). This document does not discuss questions concerning the disability and management of Down's syndrome. It also does not go into either screening for Down's syndrome in multiple pregnancies or those obtained by medically assisted procreation.

Document search was conducted over the period 1998-2006. 581 articles were analysed and 229 are cited in the document.

A multidisciplinary working panel made up of 19 experts met four times to discuss the document drafted by HAS from the review of the literature and to propose conclusions and recommendations.

Once finalized, the working document was submitted to a reading panel of 50 persons from outside the working panel, who assessed the quality of its contents and the presentation of the report.

Overall, a public health recommendation is proposed, including:

- A critical appraisal of screening for Down's syndrome in France and other countries;
- Analysis of the clinical performance and safety of screening strategies;
- Consideration of the acceptability of screening;
- Economic analysis of screening strategies from a review of the literature and modelling;
- Review of the literature on women’s preferences;
- Discussion of the ethical and organizational aspects of screening;
- A section on the positive or negative impact of a change in screening strategy.

This synopsis discusses all these factors for each screening strategy assessed.
II. EVALUATION CRITERIA AND SCREENING STRATEGIES STUDIED

Consistent with the literature, and in agreement with the working panel, the following screening strategies were evaluated:

- Combined first-trimester screening by measurement of nuchal translucency and serum markers (PAPP-A, free beta hCG);
- Two-step sequential screening with first–trimester measurement of nuchal translucency ± measurement of serum markers (PAPP-A, free beta hCG) followed by second-trimester tests of serum markers (double, triple or quadruple test) after disclosure of the first trimester screening results and calculation of risk integrating all second trimester markers;
- Independent sequential screening by first-trimester measurement of nuchal translucency ± serum markers (PAPP-A, free beta hCG) followed by second-trimester measurement of serum markers (double, triple or quadruple test) after disclosure of the first trimester screening results and calculation of risk not integrating all the second trimester screening results;
- Integrated screening by first-trimester measurement of nuchal translucency and serum markers (PAPP-A, free beta hCG) followed by second trimester measurement of serum markers (double, triple or quadruple test) with non-disclosure of first trimester screening results and calculation of risk integrating all the second trimester markers;
- Serum integrated screening by first-trimester measurement of serum markers (PAPP-A, free beta hCG) followed by second-trimester measurement of serum markers (double, triple or quadruple test) without disclosure of first-trimester screening results and risk calculation integrating all the results for second trimester screening markers;
- Contingent sequential screening with first-trimester measurement of nuchal translucency ± serum markers tests (PAPP-A, free beta hCG) followed by second trimester tests of serum markers (double, triple or quadruple test) with determination of cut-off values and first and second trimester pregnancy termination according to the intermediate risk level.

The second trimester ultrasound scan also provides important data for the different Down's syndrome screening strategies. However it was not specifically evaluated within the scope of this study.

These screening strategies were evaluated from the following criteria:

- The effectiveness of antenatal screening was defined as the capacity of a strategy to identify foetuses with Down's syndrome in consenting women. It was evaluated from the detection rates (percentage of women considered at risk among women with a Down's syndrome foetus) and false positive rates (percentage of women identified at risk during screening with an unaffected foetus).
- The safety of a screening strategy for Down's syndrome was evaluated from the number of foetal losses generated by the invasive diagnostic procedures. This number is related to the false positive rate of the strategy and the rate of foetal losses of each sampling method.
- Effectiveness was evaluated in two stages: A review of the international literature on the health economic impact of screening strategies was supplemented by simulation of the costs associated with screening strategies and the number of cases diagnosed by each of them, in the French setting. The results were presented in ratio form as cost per diagnosed case.
- Women’s preferences were taken into account in the evaluation process concerning in particular the time of screening, the clinical parameters of the different strategies and
arbitration between the risk of foetal loss due to amniocentesis and the birth of a Down's syndrome child.

- The availability of human and material resources required for screening and diagnosis for each screening strategy was assessed.
- The potential impact of each screening strategy was discussed.

These criteria form the basis of the assessment report. However the following sections only give a synopsis of the advantages and disadvantages of each individual screening strategy.

III. EVALUATION OF SCREENING STRATEGIES

In this synopsis of the performances of the different screening strategies analyzed we distinguish between the results of studies comparing different screening strategies and those evaluating a single strategy. This is because it is impossible to directly compare the performances of a first-trimester screening test assessed in one study and a second-trimester screening test determined in another because of bias due to viability (spontaneous foetal losses) and differences in the maternal age structure of the populations studied.

III.1. First-trimester combined screening by measurement of nuchal translucency and serum markers

III.1.1. Advantages

Among the 25 studies analysed evaluating the performance of first trimester combined screening alone, the detection rate varied between 73 and 100% for a false positive rate of between 2.1 and 94%, depending on chosen risk cut-off and age structure of the study population. The 3 comparative studies of different Down's syndrome screening strategies gave a detection rate of between 80 and 87% for a false positive rate of 5% for first-trimester combined screening. A meta-analysis updated in 2005 and including 11 studies gave a detection rate of 86% for a false positive rate of 5%. Taking into account uncertainties related to spontaneous foetal losses occurring between the first and second trimesters of pregnancy, the performance of first-trimester combined screening of Down's syndrome appears to be better than that of second-trimester serum screening (double or triple test).

This strategy has the advantage that it permits earlier antenatal diagnosis during the first trimester, in particular by chorionic villous sampling. If a decision is made to terminate pregnancy, this is less traumatic both physically and psychologically. This strategy also allows early discussion of the concept of Down's syndrome risk. The screening process is also relatively simple. All these points explain why this strategy was usually chosen by women questioned about their preferences.

Four of the six health economic studies that compared screening strategies for Down's syndrome in terms of cost-effectiveness concluded in favour of first-trimester combined screening although this strategy was never found to be both more effective and less expensive than the current practice (second-trimester serum screening or no screening). It often caused a lower foetal loss rate related to the diagnostic procedure, as fewer samples are required, and gave a better yield of these samples. Its cost-effectiveness ratio was however sensitive to the cost of measurement of nuchal translucency and was only “acceptable” if this measurement was integrated with the first-trimester ultrasound scan. In the modelling of screening strategies carried out in this report, the combined screening strategy made it possible to diagnose 37% more Down's syndrome foetuses.
than second trimester serum screening for a 1 to 2% increase in the total cost of screening depending on whether all the samples were taken by CVS or 50% by amniocentesis and 50% by CVS, for a participation of 100% and a false positive rate of 5%. This strategy had a cost-effectiveness ratio of from 965 to 1,930 € per additional case diagnosed compared with second-trimester serum screening but was classed worse than other strategies in terms of the number of foetal losses per diagnosed case (ratio of 0.4). This strategy always had dominant results whatever sensitivity analyses were performed (participation rate, prevalence rate).

Lastly, this strategy also provides early screening for other chromosomal abnormalities (trisomy 13, trisomy 18, Turner syndrome), certain anatomical defects and in particular cardiac defects and opens the way for screening for certain obstetric complications.

III.1.2. Disadvantages

The performance of first-trimester combined screening may however be affected by the problem of the reproducibility of ultrasound measurement of nuchal translucency. It therefore requires the implementation of a quality-assurance procedure. This procedure, which is initially qualitative (quality audit of ultrasound scans using scores or grids), and then also quantitative (follow-up of the distribution of measurements of nuchal translucency for each sonographer), may no doubt only gradually be extended to the whole of France.

Moreover, although first trimester screening for Down's syndrome has the advantage that it offers early access to antenatal diagnosis, its performance is subjected to certain time constraints. Because of variations in the concentration of first-trimester serum markers and the measurement of nuchal translucency according to gestational age, screening may only usefully be performed in the gestational age window of 11 to 13 weeks. This narrow window imposes on the one hand constraints in terms of organisation and on the other hand a different management for women who attend their first antenatal appointment at a later stage.

Among the disadvantages of first-trimester combined screening mentioned in the literature is the fact that pregnancies with foetuses affected by Down's syndrome have a higher risk of spontaneous foetal loss. Their early identification obliges women to make a decision about medical termination of pregnancy although a certain number of these pregnancies would have spontaneously aborted. However the fact that women may learn the reason for these foetal losses, which may be considered to be late as they occur after 12 weeks, may also be considered as a benefit of this strategy.

Finally, the benefit of screening for neural tube closure defects by assaying AFP during the second trimester is lost by implementation of this strategy. However, these abnormalities may be detected during the second-trimester ultrasound scan.

III.2. Integrated screening by first-trimester measurement of nuchal translucency and serum markers and second-trimester serum screening without disclosure of the first trimester results and with calculation of risk based on all the second trimester screening markers.

III.2.1. Advantages

Integrated screening is the strategy which gives the best performance. The first modelling analysis of the performance of integrated screening alone gave detection rates of between 94 and 95% for a false positive rate of 5%. These results were confirmed in 4 studies comparing the performance of different screening strategies, which gave detection rates of between 90 and 95% for false positive rates of between 2.6 and 5%. Such a strategy
may also be used to reduce the false positive rates and therefore invasive investigations to around 1%, while maintaining a high detection rate of about 85%. Assessment of Down's syndrome risk after the second-trimester sequence of screening tests also means that spontaneous foetal losses are taken into account.

This strategy also has the same potential impact on screening of other chromosomal abnormalities, anatomical malformations and certain obstetrical complications. Lastly, it allows screening for neural tube closure defects.

III.2.2. Disadvantages

The integrated screening strategy nevertheless has a certain number of disadvantages. As well as having the same difficulties as first-trimester combined screening, it does not have the advantage of early access to antenatal diagnosis. It is also a long strategy making it necessary to conduct two sequences of screening tests: first-trimester assay of serum markers and measurement of nuchal translucency followed by second-trimester tests of serum markers. It may therefore be less preferred by women. Health economic analysis by the SURUSS study recommended integrated screening (complete or serum integrated screening if the measurement of nuchal translucency was not available), as it has the lowest cost per diagnosed case and also gives the lowest foetal loss rate. On the contrary, the modelling of screening strategies conducted in this report showed that although the integrated screening strategy definitely gave the best results in clinical terms (highest detection rate, lowest foetal loss/diagnosed case ratio (0.22)) it was also the most expensive: Although this strategy increased the number of diagnosed Down’s syndrome foetuses by 54% compared to second-trimester serum screening, it also increased the total cost by 55%. Overall, the cost-effectiveness ratio of this strategy was poor as it was necessary to spend more than 40,000 € to diagnose one additional case of Down’s syndrome compared to second-trimester serum screening.

There is also a risk with this complex strategy that women drop out during screening and are lost to follow-up between the two sequences. It also has ethical problems as women are not informed about the risk of Down’s syndrome after the first trimester screening tests. In particular, it does not always guarantee the respect of the fundamental principle of personal autonomy.

III.3. Two-step sequential screening by first-trimester measurement of nuchal translucency ± serum markers followed by second-trimester serum tests with disclosure of the results of first trimester screening and risk calculation integrating all the second-trimester screening test results

Because of the lack of availability of first-trimester serum markers, the modified strategy currently used in France is based on first-trimester measurement of nuchal translucency with karyotyping advised for patients found to be at high risk, followed by second-trimester assay of serum markers with correction of results by the relative risk related to nuchal translucency.

III.3.1. Advantages

Only 2 studies evaluated the performance of two-stage sequential screening with first-trimester measurement of nuchal translucency alone: the detection rate was between 80.6 and 88% for a false positive rate of from 4.8 to 5.3%. In the 3 studies comparing this strategy with other Down's syndrome screening strategies the detection rate was between 90 and 95 % for a false positive rate of 5%. However in this case, sequential screening
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was based on one measurement of nuchal translucency and first-trimester serum markers.
In comparison, the detection rates of independent sequential screening with measurement of nuchal translucency alone during the first trimester were between 81 and 91.4% but with a false positive rate of between 7.2 and 8.6%.
Two-stage sequential screening therefore has the advantage that it has a lower false positive rate than independent sequential screening and partially takes into account the spontaneous foetal losses occurring between the first and second trimesters of pregnancy.
Finally this strategy offers the same additional benefits in terms of antenatal screening as the combined screening strategy.
Health economic analysis showed that two-stage sequential screening, in our simulation, was a dominant strategy compared to second-trimester serum screening. It effectively increased the number of detected Down's syndrome foetuses by 32 % for the same total cost. It also had a low foetal loss/diagnosed case ratio (0.25). This strategy always gave dominant results whatever sensitivity analysis was performed (participation rate, prevalence rate).

III.3.2. Disadvantages
As this strategy is based on a first-trimester measurement of nuchal translucency it has the same difficulties as first-trimester combined screening. It therefore requires the implementation of a quality-assurance system and the respect of the same time window.
Two-stage sequential screening only has the advantage of earlier antenatal diagnosis for those women considered to be at high-risk after first-trimester measurement of nuchal translucency and/or assay of serum markers. Moreover, its performance is only optimal if all women undergo first and second trimester screening tests. In this case, this strategy, which takes place over two trimesters, has the same acceptability problem as integrated screening.
Finally this strategy, which is more complex than first trimester combined screening, makes it more difficult for women to understand the procedures and information about the calculated risk of foetal Down's syndrome.

III.4. Contingent sequential screening

III.4.1. Advantages
Contingent sequential screening is the screening strategy with the highest theoretical benefits. Its modelled performances are high (detection rates ranging between 85 and 90% for false positive rates of between 1 and 3%) and it reduces the number of women who must undergo second-trimester serum screening to a low percentage.
This strategy therefore combines the advantage of the earliness of antenatal diagnosis and rapid screening for most women.

III.4.2. Disadvantages
This strategy is however more complex to organise and more difficult to understand. Moreover, because of the lack of studies on the general population it is not currently possible to make valid conclusions.
IV. NECESSARY CONDITIONS FOR CHANGES IN DOWN’S SYNDROME SCREENING STRATEGIES

IV.1. Acceptability of screening strategies

The literature on screening participation rates mainly concerns second trimester screening for serum markers. In France, studies show that screening has become increasingly acceptable to women and this has probably gone hand in hand with an improvement in the adherence of prescribing doctors: 76% of women aged less than 38 and 31% of women aged 38 years or more participated in screening in 2003 compared to 52% and 10% in 1997 respectively. Ninety-five percent of women identified to be at risk underwent antenatal diagnosis in France.

No data are currently available in 2006 for the other screening strategies evaluated in this report. Literature studies show that for antenatal screening of Down's syndrome, the understanding of the information provided by health practitioners is a fundamental factor determining the acceptability of the screening program: A lack of information and/or understanding causes confusion, in particular about the difference between a risk assessment and a definite diagnosis and about the issues involved in screening which may prevent women from making a free and informed decision about being screened or not. According to the literature, this is particularly true for women in low-income groups or born outside France.

To prevent difficulties in obtaining access to or understanding information, in particular by foreign-born or underprivileged women, this information should be given in as simplified a form as possible and mothers should be instructed verbally in order to clarify the different steps involved in each strategy as far as possible. In this respect, the HAS working panel proposes that a document is drafted to facilitate provision of this information and that the Order specifying the current procedures for collecting consent is modified. The need to train practitioners was also underlined.

IV.2. Organisational considerations

Improvement in the current screening procedure or changes in screening strategies initiated during the first trimester of pregnancy make it necessary to ensure the quality of the tests performed and the risk calculation:

- Quality of laboratory tests: For serum markers, quality control is already in place and organised by clinical laboratory specialists for second-trimester markers and the existing models may easily be transposed to measurement of the first-trimester serum markers. The feasibility of first-trimester quality control has already been studied in 12 laboratories for one year.

- Quality of measurement of nuchal translucency: Provision of first-trimester combined screening must be conditioned by the setting up of a quality-assurance program for the measurement of nuchal translucency. Its implementation must therefore be progressive and probably regional. Quality-assurance programs are an essential condition for the good reproducibility of nuchal translucency measurement and supervision of its interpretation (use of validated multiples of the median). They are based on the training of practitioners and implementation of qualitative and quantitative quality control (quality audit of ultrasound images and follow-up of distribution of nuchal translucency measurements). Multidisciplinary antenatal diagnosis centres may play an evaluation role in the implementation of quantitative quality control of nuchal translucency measurement in their geographical area.
• Quality of the risk calculation: This requirement for quality must also apply to the software used to compute the combined risk. It is necessary to evaluate them to study their validity.

Adherence of health practitioners to quality control of nuchal translucency measurement may be encouraged by using positive incentives. A revalorisation of the tariff for the first trimester ultrasound scan or institution of a separate codification may help compensate for the constraints imposed by the time required for training and the increased duration of the examination.

Setting up a quality-assurance system will facilitate collaboration between sonographers and laboratory specialists, which is essential for a screening strategy combining the results of nuchal translucency measurements and tests of serum markers (first or second trimester). The calculation of the combined risk should be made by laboratory specialists who, since 1997, have acquired the necessary experience to integrate ultrasound data by handling different reagents with their software since the setting up of second-trimester serum screening.

On the other hand, the setting up of an integrated screening strategy over two trimesters may run into coordination difficulties.

The time constraints inherent to each strategy must also be taken into account. The time window for first-trimester combined screening is limited because of the effect of gestational age on the performance of screening strategies integrating first-trimester markers. An opportunity for second-trimester screening must also be planned for women attending the first antenatal appointment at a late stage.

Forecasts about the number of foetal sonographers and the time required to generalise quality assurance to the whole of France suggest that access to first-trimester screening strategies should be restricted to those centres that have already organised this quality control. This may be considered inequitable. However, it would not be very realistic to wait until this organisation has been generalised to the whole country in particular as excellent facilities are already available in certain regions.

On the contrary, the availability of human resources for chorionic villous sampling is not a major obstacle to the implementation of first-trimester screening. This is because the choice of the foetal sampling method, chorionic villous sampling from 11 weeks of gestation or amniocentesis from 15 weeks, is made by each woman, after she has received information and advice from her gynaecologist. This choice may be influenced by the availability of experienced cytogeneticists near the woman's home, the specific technical difficulties of chorionic villous sampling, the safety of each sampling method and the speed with which diagnosis is obtained.

Lastly, in every case, it should be possible to integrate an antenatal screening strategy for Down's syndrome within the current organisation of perinatal care. For consistent monitoring of pregnancy to be maintained, general practitioner and midwives must have the opportunity to continuously manage the screening procedure and accompany women for the whole duration of this care pathway.
CONCLUSIONS

This literature review of the different aspects of screening for Down's syndrome with respect to the purpose of screening (i.e. to provide reliable information to help consenting women make an informed choice) and data obtained by simulating the economic impact of screening strategies in the French setting, make it possible to draw the following conclusions in agreement with the working and reading panels:

1. On the basis of the clinical evidence concerning efficacy and safety, economic data, acceptability for women and woman's preferences, it is recommended to propose first-trimester combined screening between 11 weeks and 13 weeks + six days of gestation, comprising measurement of nuchal translucency (according to crown-rump length) and assay of serum markers (PAPP-A and free beta hCG).

   Development of this screening strategy in France requires changes to the regulatory framework (Orders of May 27, 1997 and September 30, 1997) on antenatal screening for Down's syndrome.

   Implementation of this screening must be accompanied by a nuchal translucency quality assurance program. This quality assurance system should be based on two major approaches:

   • Training for practitioners complying with precise contract specifications for which there is already a homogeneous offer;

   • A quality control program initially based on qualitative data (quality check of ultrasound scans using a score or a grid) and gradually extending to quantitative data (follow-up of the distribution of nuchal translucency measurements), at regional or national level. This quantitative control may be organised by each of the 48 Antenatal Diagnosis Centres though this will no doubt require the allocation of new funds.

   An increase in the tariff of first trimester ultrasonography which should made conditional on the participation of sonographers in a quality-assurance program.

   The question of the availability of the offer must also be subject to detailed attention. Concerning this point, HAS underlines the need to validate the software used to assess the combined risk. Risk assessment from the measurement of nuchal translucency and serum screening tests may be conducted by laboratory specialists, sonographers or clinicians and the quality control of the scans by sonographers or prescribers.

   HAS also considers that women must be allowed to choose the method used for foetal sampling to conduct antenatal diagnosis when this is required, after receiving the consultant’s advice: chorionic villous sampling from 11 weeks of gestation or amniocentesis from 15 weeks. Before making this choice, women should be informed, perhaps during a genetic counselling session, about the specific technical difficulties involved in chorionic villous sampling, the safety of each sampling method and the time required to make a diagnosis.

2. Implementation of this strategy should not lead to the suppression of second-trimester serum screening. HAS considers that it is necessary to keep this strategy as women unable to undergo first-trimester combined screening as they were outside the time window or because a satisfactory measurement of nuchal translucency could not be made, must also have access to screening.
3. HAS considers that when the conditions for organizing first-trimester combined screening and in particular the availability of first-trimester serum, cannot be guaranteed, a two-stage sequential screening strategy, based on first-trimester measurement of nuchal translucency and second-trimester serum screening tests may be proposed to women, provided the second trimester calculation of the risk for Down's syndrome integrates the nuchal translucency result. In this case, HAS stresses the need to validate the software used to calculate risk.

4. In the current state of knowledge and taking into account the complexity of these strategies, women’s preferences and the respect of the principle of personal autonomy, integrated screening strategies over two trimesters without disclosure of the results of the first trimester tests (first-trimester nuchal translucency measurement and serum screening tests and second-trimester assay of serum markers) are not recommended.

5. Independent sequential screening, basing on an interpretable measurement of nuchal translucency and second-trimester assay of serum markers with calculation of second-trimester risk not integrating the results of all the tests carried out beforehand, is not recommended. Although this strategy results in a high detection rate, it also leads to high amniocentesis rates.

6. HAS considers that it is no longer justified to conduct antenatal diagnosis from the outset in women aged 38 years or more, without previously performing screening tests. In this age bracket, screening strategies give very high detection rates with a large reduction in foetal sampling rates.

7. Whatever strategy is considered, the working panel insists on the need to provide women with appropriate information on suitable supports about the proposed strategies. The information contained in these supports (in different languages) should enable all women to understand Down’s syndrome and inform them about existing screening strategies, the advantages/disadvantages of the proposed tests, the concept of risk and the distinction between risk and definitive diagnosis, the opportunities offered to give samples for antenatal diagnosis and medical termination of pregnancy (MTP). In no case should antenatal screening and MTP be presented as an obligation. This information will clarify women's' choices at the three stages of decision making (screening, diagnosis and MTP). Health practitioners involved in antenatal care must also be given information and training because of this change in screening strategy.

8. The population impact of the changes in screening strategy should be evaluated.

9. Finally, concerning future developments and changes in screening strategies for Down’s syndrome, HAS proposes that:
   - Because of their potential performances, integrated screening strategies with first and second trimester tests (first-trimester nuchal translucency test and serum screening and second-trimester serum screening) may be implemented within managed and time-organised care pathways (research programs) and after providing women with complete and appropriate information;
   - The future role of new first-trimester ultrasound and serum markers for antenatal screening of Down's syndrome is currently the subject of further research.
The drafting of regulatory texts on these changes in screening strategy must take future progress in our understanding of screening and antenatal diagnosis of Down's syndrome into account.
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D’ Philippe MUSSAT, paediatrician, LE BLANC-MESNIL
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Mrs Geneviève PERESSE, sonographer, ECHIROLLES
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D’ Marc ROGER, laboratory specialist, PARIS
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D’ Brigitte SIMON-BOUY, cytogeneticist, LE CHESNAY
Professor Peter SOOTHILL, gynaecologist-obstetrician, BRISTOL, ROYAUME-UNI
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D’ Claude TALMANT, sonographer, LA CHAPELLE SUR ERDRE
D’ Françoise VENDITTELLI, epidemiologist, CLERMONT-FERRAND
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Dr. Bernard DINGEON did not wish to be associated with the conclusions of this report. He was able to make his objections during the review process. We thank him for his participation in the reading panel.