First-trimester prenatal screening for Down syndrome and other aneuploidies

AGENCE D'ÉVALUATION DES TECHNOLOGIES
ET DES MODES D'INTERVENTION EN SANTÉ

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First-trimester prenatal screening for Down syndrome and other aneuploidies

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by Alicia Framarin

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For information about this publication or any other AETMIS activity, please contact:

Agence d'évaluation des technologies et
des modes d'intervention en santé
2021, avenue Union, bureau 1040
Montréal (Québec) H3A 2S9

Tel.: (514) 873-2563
Fax: (514) 873-1369
e-mail: aetmis@aetmis.gouv.qc.ca
http://www.aetmis.gouv.qc.ca

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MISSION

The mission of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) is to contribute to improving the Québec health-care system and to participate in the implementation of the Québec government's scientific policy. In order to accomplish this, the Agency advises and supports the Minister of Health and Social Services as well as the decision-makers in the health-care system with respect to the assessment of health services and technologies. The Agency makes recommendations based on scientific reports assessing the introduction, diffusion and application of health technologies, including technical aids for disabled persons, as well as the modes of providing and organizing services. The assessments take into account multiple factors, such as efficacy, safety and efficiency, as well as ethical, social, organizational and economic impact.

FOREWORD

FIRST-TRIMESTER PRENATAL SCREENING FOR DOWN SYNDROME AND OTHER ANEUPLOIDIES

In 1999, the Conseil d'évaluation des technologies de la santé (CETS), subsequently renamed the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), published an assessment report on the issues relating to second-trimester prenatal Down syndrome screening and diagnosis. The report, which was prepared at the request of the Ministère de la Santé et des Services sociaux, concluded, among other things, that second-trimester prenatal serum screening is a less expensive and more effective option than diagnosis by amniocentesis in women aged 35 and older and a valid option for all pregnant women, regardless of their age.

There has been a rapid succession of scientific and technological advances in the area of prenatal screening for Down syndrome and other chromosome abnormalities, and this has led to practice changes in Québec. AETMIS consequently deemed it necessary to examine the efficacy and the effectiveness of first-trimester prenatal screening. This assessment report looks at the efficacy and the effectiveness of first-trimester serum marker and ultrasound screening and at the different issues relating to the implementation of such screening in Québec.

AETMIS feels that, although the efficacy of first-trimester prenatal screening is satisfactory, its effectiveness has yet to be demonstrated, as indicated by numerous published studies that have examined this aspect. Studies comparing the efficacy of first-trimester screening with that of second-trimester screening are currently under way. If the two prove to be of equal efficacy, pregnant women would nonetheless prefer first-trimester screening, since it permits an earlier diagnosis. In this report, we will also stress the importance of the information to be given to women so that they can make informed decisions.

In conclusion, given the available data, AETMIS does not recommend implementing wide-scale first-trimester prenatal screening in Québec. However, it does feel that the effectiveness, costs and implementation modalities should be assessed or determined by means of research projects in settings where quality service can be provided.

In disseminating this report, AETMIS wishes to provide the best possible information to the decision-makers at the different levels in Québec's health-care system who are concerned by this matter.

Renaldo N. Battista
President and Chief Executive Officer

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Dr. Ségolène Aymé
Director of Research, Institut national de la santé et de la recherche médicale (INSERM), Paris

Lola Cartier
Genetic Counsellor, McGill University Health Centre, Montréal

Dr. Valérie Désilets
Obstetrician, Clinical Director, Prenatal Diagnosis Program, McGill University, Montréal

Dr. Jacques Massé
Medical Biochemist, Cité de la Santé de Laval, Laval

Dr. Jacques L. Michaud
Medical Geneticist, Service de génétique médicale, Hôpital Sainte-Justine, Montréal

SUMMARY

Introduction

Down syndrome, or trisomy 21, is the most common viable chromosome abnormality. The clinical presentation is variable, but the phenotype is characteristic and is always accompanied by a certain amount of mental retardation. Its incidence in the population is 1 per 770 live births, or 1.3 per 1,000 live births. The incidence increases gradually with maternal age up to the age of 35 and very quickly thereafter. In Québec, as elsewhere in the world, pregnant women aged 35 and older are offered amniocentesis for the purpose of diagnosing Down syndrome and other chromosome abnormalities. This program has been in place since 1976. However, although the risk of giving birth to a child with Down syndrome is higher after the age of 35, most affected children are born of mothers under the age of 35, since there are fewer deliveries after this age. Furthermore, amniocentesis is an invasive procedure that carries a risk of complications, including the iatrogenic loss of an unaffected fetus. To improve the performance of prenatal screening and diagnosis of Down syndrome and other aneuploidies (abnormal numbers of chromosomes) and to reduce the number of amniocenteses, several techniques have been developed. Some of them, such as second-trimester serum marker screening, are routinely used in several countries and in other Canadian provinces.

In 1999, the Conseil d'évaluation des technologies de la santé (CETS), subsequently renamed the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), published an assessment report of the issues relating to second-trimester prenatal Down syndrome screening and diagnosis [CETS, 1999]. The report concluded that prenatal diagnosis by amniocentesis offered to women aged 35 and older at the time of delivery is more expensive and less effective than second-trimester maternal serum screening. CETS examined the ethical issues surrounding prenatal screening and stressed, in its recommendations, that the offer of prenatal Down syndrome screening and diagnosis should be flexible enough to adapt to new scientific and technological advances.

According to recent literature and based on current practices, first-trimester screening has been adopted in various countries. In Québec, first-trimester prenatal Down syndrome screening is presently becoming more widespread, this in the absence of clear standards and quality control mechanisms for this practice. This report is a review of the published scientific literature on first-trimester prenatal screening for Down syndrome and other aneuploidies.

First-trimester maternal serum markers

Maternal serum markers, measured during the first trimester, combined with maternal age can reportedly detect between 56 and 67% of cases of Down syndrome (61% on average), with a 5% false-positive rate. This performance only concerns singleton pregnancies. It seems comparable to that of second-trimester marker screening, although most studies have involved high-risk pregnant women and do not take the spontaneous loss of Down syndrome fetuses between the first and second trimester into account. The only study that has compared first-trimester and second-trimester maternal serum screening suggests that second-trimester screening is superior. These findings would need to be confirmed by larger studies, at least two of which are currently under way. While they may be of equal performance, first-trimester screening permits an earlier diagnosis. It does, however, have the disadvantage of providing an unnecessary diagnosis of Down syndrome,

since in such cases, the pregnancy terminates spontaneously before term in a higher percentage of women.

First-trimester ultrasound

Ultrasound is performed during the first trimester (between the 10th and 14th week of pregnancy) in order to measure nuchal translucency, i.e. the subcutaneous space between the fetal cervical spine and the overlying skin. When it is ≥ 3 mm (between 2.5 and 4 mm, depending on the study) or above the 95th percentile for the gestational age, it indicates a high risk of Down syndrome or of another aneuploidy. The mean detection rate was 69% in studies involving high-risk populations and 66% in those involving mixed or unselected populations. The detection rate is 80% when the risk is assessed by nuchal translucency measurement combined with maternal age.

As is the case with serum markers, this rate could be lower if the prevalence of Down syndrome at term, rather than the first-trimester prevalence, were taken into account. The differences observed between studies and between centres probably reflect the difficulties encountered when using nuchal translucency measurement outside of tertiary-care centres or experimental settings, in the absence of specific training and practice monitoring programs. A nuchal translucency measurement is obtained in 82 to 100% of cases. The success rate of the ultrasound technique is higher when there is no limit on the additional time required to measure nuchal translucency. It is also higher in studies in which transvaginal ultrasound is performed after an unsatisfactory transabdominal nuchal translucency measurement. It is 100% when a 3D vaginal technique is used. Studies report a repeatability coefficient of 0.22 to 1.04 mm. These differences have major repercussions on the risk calculation.

To improve the effectiveness of nuchal translucency measurement, certain conditions must be met. They are summarized in a paper by Nicolaides et al. They include, among others: 1) appropriate practical training for sonographers and auditing their results; 2) the availability of good-quality equipment with calipers that are accurate to within a decimal point; 3) making the measurement between 11 weeks and 13 weeks 6 days with the fetus in the neutral position; 4) the option of using the transvaginal approach when the measurement cannot be obtained transabdominally [Nicolaides et al., 2000].

Increased nuchal translucency when the karyotype is normal may indicate the presence of other fetal malformations or pathologies, especially cardiac malformations. In addition, the risk of the spontaneous abortion of karyotypically normal fetuses increases proportionately to the increase in nuchal translucency.

The combined test: combined use of first-trimester serum and ultrasound markers

Studies of the combined use of first-trimester serum and ultrasound markers report detection rates of 70 to 100%. However, at such detection rates, the combined test does not reduce the number of false positives. Two prospective, multicentre studies evaluating the performance of screening using the first-trimester combined test compared to that of second-trimester serum marker screening are currently under way in the United States and in Europe.

The integrated test (first and second trimesters)

The integrated test (first and second trimesters of pregnancy), which combines the results for the first-trimester serum markers and nuchal translucency and the results for the second-trimester serum markers into a single risk estimate, can reportedly detect 85% of Down syndrome cases, with a false-positive rate of less than 1%. These theoretical results were derived from a mathematical model and have never been subjected to a published clinical evaluation involving a cohort of patients. Since it includes an alpha-fetoprotein (AFP) assay, the integrated test can also be used to screen for open neural tube defects. Apart from clinical performance, it should be stressed that integrated screening generally takes two to five weeks, a long period of time that can cause a great deal of anxiety in the pregnant woman. By communicating the results as they become available, one can resolve the problem created by this very long wait. The mother can thus be immediately reassured or terminate the pregnancy earlier. However, it should be pointed out that this sequential method is less accurate, since it yields more false-positive results.

Other methods being developed

The level of beta-core fragment of human chorionic gonadotropin (hCG) and the urine estriol level have been investigated as second-trimester urine markers. Screening based on urine hyperglycosylated hCG and total urine hCG measurements between the 11th and 22nd week of pregnancy is reported to yield a detection rate of 79%, with a 5% false-positive rate. The advantage of these tests is that they can reportedly be used both during the first and second trimesters of pregnancy. This screening modality is still in the experimental stage.

Another promising technique, but one which is still investigational, is the search for fetal cells or fetal DNA in maternal blood. This technique can reportedly be used not only for the prenatal diagnosis of diseases in the fetus, but also for detecting certain diseases in the mother during pregnancy, such as preeclampsia, or after pregnancy, such as autoimmune diseases.

Women's perspective on Down syndrome screening

Published data show that, when given the option, most women prefer first-trimester screening because the period of uncertainty is shorter and because they can terminate the pregnancy earlier, before fetal movements can be perceived, and with a lower risk of complications. False-positive results cause a great deal of anxiety in pregnant women and lead to the increased use of invasive diagnostic techniques, such as amniocentesis, which carry a risk of iatrogenic loss of unaffected fetuses. Multiple testing also has repercussions on costs. A false-positive result can affect a woman's decision to participate in screening during a subsequent pregnancy and could also lead to the voluntary termination of pregnancy as a result of the woman not clearly understanding the significance of the test.

False-negative results can have psychological effects on the parents, and they can also experience more difficulty adapting to their parental role, even many years after the birth of an affected child. However, very few studies have examined this. As well, false-negative results seem to undermine public confidence in screening. Although many women agree to undergo prenatal Down syndrome screening, it seems that they are not given enough information to make an informed decision regarding their

participation in such screening when the time comes. However, they attach fundamental importance to the quality of this type of information.

The perspective of health-care professionals

A Finnish study reports that most physicians, regardless of their specialty, believe that serum-based Down syndrome screening and ultrasound screening for malformations should be offered to all pregnant women in order to prevent the birth of a handicapped child or to enable the parents to better prepare for the birth of an affected child, and in order to reduce the costs associated with managing handicapped individuals. These two types of screening were already being performed in Finland when the survey was conducted. However, the respondents indicated that, in their opinion, such screening had two major disadvantages, namely, the anxiety that false-positive results cause in women and the pressure on them to abort at a point when the pregnancy is already advanced, which can be emotionally stressful. Most of the respondents did not think that prenatal Down syndrome screening increases negative attitudes toward affected individuals, while for some of the other respondents, it could. The new screening modalities offer the advantage of accessibility, better selection of candidates for amniocentesis, and an additional option for women aged 35 and older, who are disinclined to undergo an invasive diagnostic procedure.

The position of professional associations and clinical guidelines

In 1999, the American College of Obstetricians and Gynecologists (ACOG) considered that, while promising, first-trimester prenatal screening for chromosome, cardiac or other abnormalities using nuchal translucency alone or in combination with serum markers, was still investigational. The technique for measuring nuchal translucency and the very definition of nuchal translucency need to be standardized, and until studies confirm the effectiveness of such screening, it is not recommended for routine clinical use. To date, the ACOG position remains unchanged. In 1999, the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) recommended that second-trimester serum screening programs for Down syndrome and neural tube defects be set up across the country and that they be accompanied by mechanisms to ensure the continuing education of health-care providers and consumers, and the evaluation and quality assurance of these programs.

The Canadian Guidelines for Prenatal Diagnosis states that *"[s]creening for chromosomal anomalies based on biochemical markers should only be considered within a comprehensive screening and prenatal diagnosis program including interpretation, education, and follow-up counselling"*. As specifically regards ultrasound markers, the SOGC states that the *"[p]rediction of the risk for fetal trisomies based on soft signs should conform to accepted criteria for a screening program and should only be done where facilities exist for adequate follow-up."* Further studies should be conducted to determine how ultrasound signs *"can be combined with other information such as maternal age or maternal serum screening to provide risk estimates."* In Québec, a report prepared by an ad hoc committee and approved by three medical associations recommends the rapid implementation of a second-trimester prenatal screening program and the assessment, in a university setting, of first-trimester screening.

The perspective of Down syndrome associations

The Canadian Down Syndrome Society expressed its position regarding prenatal genetic testing in May 1999. It feels that prenatal Down syndrome screening, the objective of which is to detect affected fetuses and terminate pregnancies, can adversely affect the quality of life of individuals with Down syndrome in our community. This could happen if this approach leads to a reduction in funding and support services for these individuals and if society in general adopts a negative attitude toward them. However, the Society does support screening if performed with a view to providing improved care by enabling parents and health professionals to better prepare for the birth of an affected child. Participation in screening should be voluntary and be based on quality genetic counselling. Parents should be given enough time to decide if they wish to proceed with the testing. The Society suggests giving parents the opportunity to speak to parents of children with Down syndrome.

The ethical issues

Prenatal screening and diagnosis raise various ethical issues which pregnant women and couples, health-care professionals, society and the public authorities need to address. Down syndrome screening and diagnosis do not provide a therapeutic option, since the only possible preventive measure is abortion. In this context, it is essential that participation by pregnant women and couples in Down syndrome screening be voluntary, and they should participate only if they can count on quality, objective, nondirective genetic counselling. Other ethical issues, especially that underlying the debate over selection of the unborn, also accompany prenatal screening and diagnosis. This debate is all the more crucial in the case of Down syndrome, since prenatal diagnosis does not provide any information on the degree of mental retardation or the presence or absence of serious malformations. In addition to this problem, there is the issue of the iatrogenic loss of unaffected fetuses. Lastly, prenatal screening raises the possibility of reallocating resources, which could result in a cut-back in services for managing Down syndrome individuals or in support services for their families.

Conclusions

- The efficacy (under experimental conditions) of the different first-trimester prenatal screening modalities for Down syndrome and other aneuploidies is satisfactory, but it needs to be confirmed because of the methodological limitations of most of the studies. Despite the numerous studies involving more than 150,000 pregnancies, there are still some questions regarding effectiveness, especially that of nuchal translucency measurement in nonexperimental conditions.
- At this time, it is impossible to state whether first-trimester or second-trimester screening is superior in terms of efficacy.
- Different first-trimester prenatal screening modalities are already available in Québec, both in the public and private sector.
- First-trimester prenatal screening permits an earlier diagnosis than second-trimester screening. Consequently, pregnant women prefer this approach.
- Implementing first-trimester screening will require changes to current prenatal care practice, mainly with regard to the week of pregnancy during which the pregnant woman's first medical visit takes place, the

number of ultrasounds required and when, during the pregnancy, ultrasound is performed. Some of these changes are already being instituted in Québec.

- Prenatal Down syndrome screening should be included with all other prenatal screening activities and take into consideration the other diseases that these techniques might or might not be able to detect.

Recommendations

- Based on the current state of knowledge, implementing **wide-scale** first-trimester screening in Québec cannot be recommended. However, it is essential that current practices be guided in order to ensure the quality of the services provided. First-trimester screening should be restricted to university hospitals which meet all the requirements for providing quality service and which agree to be evaluated. The primary objective of the evaluation would be to determine the effectiveness of the different modalities in the Québec context. It should also make it possible to define the characteristics of the population and the service network and to determine the professionals' training needs regarding the techniques and genetic counselling, and the availability of suitable equipment and the costs associated with screening in Québec. It would also serve to determine the main aspects of developing and implementing quality control mechanisms, should the practice be expanded.
- The conclusions of the 1999 CETS report, which examined second-trimester screening and diagnosis, still hold[1]. Implementing second-trimester screening will make it possible to offer serum marker screening to all pregnant women who want it. It may also serve to set up genetic counselling services, which will be useful for all other types of prenatal screening and diagnosis, as well. Eventually, it may become a complementary approach to or be replaced by first-trimester screening. The results of research currently under way will make it possible to compare first-trimester screening and second-trimester screening and their usefulness when used alone or in combination.

1. Those conclusions still hold, even though the economic analysis of second-trimester screening was not updated, as this was not one of the objectives of this report, and though the quadruple marker should replace the triple marker.

Since the results of the SURUSS* trial (Serum, Urine and Ultrasound Screening Study) were being published right when we sent this assessment report to press, the report's conclusions and recommendations need to be discussed in light of those results.

As regards the conclusions, we have expanded upon the second one:

- Since the efficacy of first-trimester screening (combined test) and that of second-trimester screening (quadruple test) are comparable, it cannot, at this time, be stated that either modality is superior to the other.

In addition, the results of the SURUSS trial confirm the recommendations of this assessment report, mainly with regard to:

- The usefulness of instituting second-trimester prenatal screening in Québec; and
- The need to first limit the practice of first-trimester screening to specialized centres in order to determine its effectiveness, feasibility, costs and organizational aspects in the Québec context.

Furthermore, new knowledge is to be added to this assessment, specifically:

- It is important to examine the conditions for the practice of nuchal translucency measurement, especially the technical performance of ultrasound equipment (makes and models).
- When used alone, certain markers, mainly nuchal translucency measurement, do not seem to be very effective.
- From a practical standpoint, the integrated test is effective, and the integrated test exclusively with first- and second-trimester serum markers can yield a good performance.

However, as the authors point out, studies under way will need to confirm the feasibility and acceptability of the integrated test.

* Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). Health Technol Assess 2003;7(11).

GLOSSARY

Abortion:
the spontaneous or induced expulsion of a fetus before its viability date. In this report, "abortion" and "fetal loss" are sometimes used synonymously.

Aneuploidy:
an abnormal number of chromosomes. It is due to the absence of a chromosome or the presence of an extra chromosome. The normal human karyotype has 46 chromosomes, 22 pairs of somatic chromosomes and one pair of sex chromosomes.

Detection rate:
the detection rate reflects a test's sensitivity, that is, its ability to detect affected individuals. It is closely associated with the risk cut-off level used and the false-positive rate, but it is independent of the prevalence of Down syndrome (see Appendix A).

False-negative rate:
the proportion of affected pregnancies considered to be at low risk upon screening.

False negatives:
all affected cases not detected during screening (see Appendix A).

False-positive rate:
the proportion of unaffected pregnancies considered to be at high risk upon screening. This rate is independent of the prevalence of Down syndrome and is equal to the complement of specificity (1 – specificity) (see Appendix A).

False positives:
all cases which are unaffected but which are considered at high risk upon screening (see Appendix A).

High risk after screening:
the estimated risk is greater than or equal to the chosen risk cut-off level. In the case of Down syndrome screening, the risk cut-off level generally used is between 1:250 and 1:385.

Iatrogenic fetal loss:
in this report, iatrogenic fetal loss will refer solely to the loss of unaffected fetuses due to a procedure aimed at diagnosing this disease.

Multiple of the median (MoM):
in a pregnant woman, the concentration of a given serum marker divided by the median value of the concentration of that marker in all pregnant women of the same gestational age, after eliminating the pregnancies characterized by a disease that can affect serum marker levels. Depending on the test, an abnormal value will be expressed as a fraction (e.g., 0.5) or as a multiple (e.g., 2.0) of the median value.

Phenotype:
the outward manifestation of a given individual's constitution resulting from the interaction between his or her genetic baggage and his or her environment.

Risk:
in this report, risk is the relationship between the number of affected and unaffected pregnancies. It is expressed as a ratio (e.g., a risk of 1:20 means 1 affected pregnancy for 20 unaffected pregnancies) or a proportion (e.g., a risk of 1/21 means 1 affected pregnancy out of a total of 21 pregnancies).

Risk cut-off level:
a value which, during screening, serves to distinguish between high and low risk.

Screening:
the identification of a health problem in individuals who appear to be in good health. In the specific context of this report, "screening" refers to tests performed in pregnant women in order to identify those who are at high risk for carrying a child with Down syndrome. Detecting a high risk does not confirm a diagnosis but stresses the need to perform additional diagnostic tests.

Success rate:
the technical ability to obtain the desired measurement, e.g., the proportion of fetuses in whom a nuchal translucency measurement can be obtained.

Trisomy:
the presence of three, rather than two, homologous chromosomes.

LIST OF ABBREVIATIONS

AFP:	Alpha-fetoprotein
β-hCG:	β-subunit of human chorionic gonadotropin
CI:	Confidence interval
DS:	Down syndrome
FISH:	Fluorescent *in situ* hybridization
FMF:	Fetal Medicine Foundation
FN:	False negatives
FP:	False positives
hCG:	Human chorionic gonadotropin
MACS:	Magnetic-activated cell sorting
MoM:	Multiple of the median
NT:	Nuchal translucency
PAPP-A:	Pregnancy-associated plasma protein-A
PCR:	Polymerase chain reaction
ST:	Serum tests
TA:	Transabdominal ultrasound
TP:	Termination of pregnancy
TV:	Transvaginal ultrasound
uE3:	Unconjugated estriol

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1

INTRODUCTION

Down syndrome, or trisomy 21, is the most common viable chromosome abnormality. Its clinical presentation is variable, but the phenotype is characteristic and is always accompanied by a certain amount of mental retardation. Its incidence in the population is 1 per 770 live births, or 1.3 Down syndrome births per 1,000 live births. The incidence gradually increases with maternal age up to the age of 35 and much more quickly thereafter. In Québec, as elsewhere in the world, pregnant women aged 35 and older are advised to undergo amniocentesis for the purpose of diagnosing Down syndrome and other chromosome abnormalities. In Québec, the program has been in place since 1976. However, although the risk of giving birth to a Down syndrome child is higher after the age of 35, since there are fewer births after this age, most affected children are born to mothers under this age. Thus, fewer than 40% of Down syndrome fetuses can be identified with this diagnostic method. Furthermore, amniocentesis is an invasive procedure with the potential for complications, the most serious of which is the iatrogenic loss of an unaffected fetus.

To improve the diagnostic performance for Down syndrome and to reduce the number of amniocenteses, a number of techniques have been developed. Some of them, such as second-trimester maternal serum marker screening, are routinely used in several countries and in other Canadian provinces.

In 1999, the Conseil d'évaluation des technologies de la santé (CETS), subsequently renamed the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS), published an assessment report on the issues relating to prenatal Down syndrome screening and diagnosis [CETS, 1999]. In its assessment, CETS mainly examined second-trimester maternal serum markers, a technique recognized both for its efficacy and feasibility. The report found that prenatal diagnosis by amniocentesis offered to women aged 35 and older at the time of delivery was more expensive and less effective than second-trimester prenatal screening and diagnosis. The report raised and examined various ethical issues which pregnant women and couples, health-care professionals, society and the public authorities need to address. In its conclusion, CETS stated that second-trimester maternal serum screening should be available to all pregnant women in Québec, regardless of their age, but that their participation should be voluntary and be based on complete, high-quality information. Women aged 35 and older would maintain their right to immediate access to amniocentesis without prior screening and be free to avail themselves thereof.

However, since prenatal screening methods are evolving at a very rapid pace, CETS emphasized, in its recommendations, that the offer of prenatal Down syndrome screening and diagnosis should be flexible enough to adapt to new scientific and technological advances. In fact, based on recent literature and current practices, first-trimester screening has been widely adopted in several countries.

In Québec, first-trimester prenatal Down syndrome screening is becoming more widespread, this in the absence of uniform standards and quality control mechanisms for this practice. This is why the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) decided to examine the different methods of first-trimester prenatal screening and diagnosis of Down syndrome and other aneuploidies (abnormal numbers of chromosomes). This report is a review of the published scientific studies on the subject.

2

METHODOLOGY

We reviewed the published scientific data on four modalities of first-trimester prenatal screening for Down syndrome and other aneuploidies: 1) first-trimester maternal serum marker screening; 2) first-trimester ultrasound nuchal translucency measurement; 3) combined first-trimester serum markers and ultrasound; and 4) the integrated screening test (first and second trimesters).

A search for the relevant literature was performed in Medline, Current Contents and the Cochrane Database using the following keywords: *prenatal screening* or *prenatal diagnosis* and *Down syndrome* or *trisomy*. We included papers published up until December 2001, plus certain more recent relevant articles. We only selected articles published in English, French and Spanish. We also consulted the database of the International Network of Agencies for Health Technology Assessment (INAHTA). Special attention was paid to the possible duplication of data, since a certain number of publications present overlapping study results. In such cases, we considered only the study published last. In addition, we consulted articles and syntheses on first-trimester prenatal screening. To complete our review of the relevant literature, we consulted the lists of references in the selected articles and examined information published on the Internet.

We only selected studies that indicated the detection rates reported for aneuploidy and Down syndrome screening. Of the studies of serum markers used alone or in combination with ultrasound, we chose those concerning two serum markers, namely, the free β-subunit of chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A). We classified the studies according to whether they were retrospective or prospective and according to the study population, i.e., a mixed or an unselected population (low-risk and high-risk) or a population of women at high risk for carrying a Down syndrome child. To assess the efficacy of the different techniques, we considered the two biases encountered most frequently in studies, namely, verification bias (which does not take voluntary pregnancy terminations into account in cases of affected fetuses, which would have aborted spontaneously in any event) and the bias introduced by the fact that not all pregnancies are followed up to the time of delivery.

3

DESCRIPTION OF THE DIFFERENT PRENATAL SCREENING AND DIAGNOSTIC TECHNIQUES

3.1 Screening techniques

Prenatal screening for Down syndrome and other aneuploidies comprises the techniques proposed to all pregnant women for the purpose of identifying those at increased risk for giving birth to an affected child. A high risk does not indicate that the fetus is affected but does point to the need to confirm the diagnosis with further testing. The risk cut-off level chosen will influence the detection rate and the false-positive rate. For a given detection rate and a given false-positive rate, the risk cut-off level varies according to the trimester of pregnancy. The risk of carrying a Down syndrome fetus is higher at the beginning of a pregnancy than at term because of the spontaneous loss of affected fetuses, which can occur at any time during pregnancy. For example, for a 35-year-old woman, the risk of having a Down syndrome fetus during the second trimester is 1:290, but it is 1:380 at term [Cuckle and Wald, 1990].

Prenatal screening can be done:

a) by measuring the levels of maternal serum markers in a maternal blood specimen, and

b) by ultrasound.

Other techniques are still in the experimental stage, such as the urinary β-core assay, the β-core being a breakdown product of hCG, specifically, the β-hCG subunit.

3.1.1 Screening using maternal serum markers

In the second trimester, the combined use of three biochemical markers (AFP, uE3 and hCG) found in maternal blood is the basis of the serum test, which is referred to as the "triple test" or "triple marker". To perform these assays, a blood sample must be taken from the pregnant woman between the 15th and 18th week of gestation. The triple test is used to screen for pregnancies at risk for Down syndrome, for trisomy 18 (Edwards' syndrome), without additional tests, but with a different protocol, and for open neural tube defects. This technique has an overall detection rate of 65%, with 5% false positives when the risk cut-off level is between 1:250 and 1:380 [Wald et al., 1997].

The triple test has been adopted in most of the existing screening programs, with its variants, i.e., the measurement of total intact hCG or of its two subunits, α and β. Adding a fourth marker, inhibin-A, yields a detection rate of 76 to 79%, with 5% false positives [Wald et al., 1996a]. These tests offer the advantages of safety and speed, but their use during the second trimester of pregnancy delays the detection of chromosome abnormalities and the termination of pregnancy, if applicable. Furthermore, assuming a false-positive rate of 5%, 5% of women will have to undergo an amniocentesis, which carries an inherent risk, namely, the potential loss of an unaffected fetus.

First-trimester serum marker screening is based on the measurement of two markers, PAPP-A and the free β-subunit of chorionic gonadotropin (β-hCG) in the mother's serum. The blood samples are withdrawn between the 8th and 13th week of gestation, but the ideal time is the 11th week. It is this specific screening modality that is examined in this literature review. A detailed description of first-trimester serum marker screening and its performance is provided in Chapter 4.

3.1.2 Ultrasound screening

First-trimester ultrasound screening consists in measuring nuchal translucency, the subcutaneous space between the fetal cervical spine and the overlying skin, between the 10th and 14th week of gestation. When it is ≥ 3 mm or above the 95th percentile for the gestational age, it indicates a high

risk of Down syndrome and other aneuploidies and fetal malformations. This report specifically examines this ultrasound screening modality. A detailed description of this method and its performance is provided in Chapter 5.

A new ultrasound marker is presently being investigated, the absence of nasal bone, or nasal hypoplasia, as detected by ultrasound between the 11th and 14th week of pregnancy. Nasal hypoplasia is more frequent in Down syndrome fetuses and irrespective of the nuchal translucency measurement. Adding this marker to the others could improve the detection rate and reduce the number of false positives during first-trimester ultrasound screening [Cicero et al., 2001].

Ultrasound performed during the second trimester, that is, after the 14th week of pregnancy, can reportedly detect a certain number of ultrasound markers, such as nuchal fold thickness (≥ 6 mm), choroid plexus cysts in the brain, the shortening of long bones (femur and humerus), and cardiac and gastrointestinal abnormalities (duodenal atresia). The performance of second-trimester ultrasound aneuploidy screening, alone or combined with serum markers, has not been demonstrated, and its widespread use is problematic [Wald et al., 1997].

Smith-Bindman et al. also arrived at this conclusion after a meta-analysis of 56 studies of second-trimester ultrasound and its ability to detect Down syndrome. The studies involved 1,930 fetuses with Down syndrome and 130,365 fetuses without Down syndrome. Taken as a whole, second-trimester ultrasound markers reportedly permit a detection rate of 69% (95% CI: 63 to 75%). However, in isolation, each of these markers has a low performance, and abnormalities are often detected late (i.e., between the 17th and 20th week of pregnancy). A number of studies show that combining ultrasound markers and other structural abnormalities increases the accuracy of ultrasound screening. However, the results are mixed, and it is impossible to determine which markers should be measured in order to obtain the best results [Smith-Bindman et al., 2001]. The performance of second-trimester ultrasound as a prenatal aneuploidy screening method is poor. However, the ultrasound is used systematically in Québec and Canada to examine overall fetal morphology and to detect various malformations, especially of the neural tube, and other polygenic malformations. In this regard, it leads to a greater number of requests for amniocentesis.

3.2 Diagnostic techniques

Prenatal diagnosis of Down syndrome is based on karyotyping fetal cells obtained by amniocentesis or chorionic biopsy and is intended for pregnant women at high risk due to their age at the time of delivery or for those considered to be at high risk as determined by one of the screening modalities described above.

3.2.1 Amniocentesis

Amniocentesis is performed to obtain desquamated fetal skin cells, which are used to diagnose Down syndrome and other chromosome abnormalities. The fetal cells obtained are cultured and handled in such a way as to obtain a karyotype, that is, a complete chromosome map. Amniocentesis performed between the 15th and 19th week of pregnancy has become a standard second-trimester prenatal diagnostic procedure. The sensitivity and specificity of amniocentesis for Down syndrome are greater than 99%. The rare errors are due to sample quality, either because maternal rather than fetal cells are cultured or because the cells are contaminated during the puncture [Gosden, 1992]. The maternal

risks associated with this procedure include infection (amnionitis) (1 case in 1,000), amniotic fluid leakage and obstetrical bleeding. Minor complications are more frequent (2 to 5%). They include slight amniotic fluid leakage, uterine contractions and abdominal pain [Elias and Simpson, 1993; Dick et al., 1996]. The risk of fetal loss after amniocentesis is approximately 0.5 to 1% [Tabor et al., 1986]. However, the risk can be reduced if ultrasound is used during the procedure and if it is performed by experienced professionals [Jauniaux et al., 2000]. The other risks for the fetus during amniocentesis are puncture wound, infection, respiratory distress syndrome and isoimmunization [Tabor et al., 1986; USPSTF, 1996].

The practice of first-trimester (between the 11th and 14th week of pregnancy) amniocentesis began in 1980 as a possible alternative to chorionic biopsy for the purpose of early prenatal diagnosis. From a technical standpoint, the procedure is identical to that performed during the second trimester. However, the small amount of amniotic fluid available before the 13th week increases the risk of fetal injury. A randomized, pan-Canadian, multicentre study showed a significant increase in fetal losses (7.6% vs. 5.9%, difference, 1.7%; p = 0.012), in clubfoot (1.3% vs. 0.1%; p = 0.0001), and in slight amniotic fluid leakage before the 22th week of gestation (3.5% vs. 1.7%; p = 0.007) after first-trimester amniocentesis compared to second-trimester amniocentesis [CEMAT, 1998]. Thus, early amniocentesis is not the least iatrogenic procedure there is, if one wishes to avoid fetal losses. In addition, a meta-analysis published in the Cochrane Library and updated in 1998 concludes that while early amniocentesis (between the 9th and 14th week of pregnancy) causes more spontaneous abortions and more clubfoot than transabdominal chorionic biopsy, the latter procedure also poses more technical problems (sampling failure, multiple punctures, need for a second specimen) and a greater risk of false-positive and false-negative results because of karyotype abnormalities specific to placental and fetal cells, respectively [Alfirevic, 2002].

There is presently very little information on the risk associated with amniocentesis performed between the 13th and 15th week of pregnancy, when a prenatal diagnosis should be made after first-trimester screening [Goldberg and Norton, 2000]. It should be noted that, when performing an amniocentesis at 16 weeks of pregnancy, and given that the cytogenetic analysis takes an average of 14 days, the pregnant woman will not receive the result until after the 18th week.

3.2.2 Chorionic biopsy

Chorionic biopsy, which was developed in the late 1960s, consists in removing small pieces of placental chorionic tissue in order to obtain viable cells, which are cultured for the purpose of a cytogenic analysis. Chorionic biopsy permits first-trimester prenatal diagnosis. It can be performed transabdominally or transvaginally.

The risks to the mother are the same as those posed by amniocentesis, namely, amniotic fluid leakage, hemorrhage, infection and intra-abdominal lesions [Elias and Simpson, 1993; Dick et al., 1996]. However, a biopsy performed after the 10th week of pregnancy poses very minor risks [Goldberg and Norton, 2000; Wilson, 2000], but if it is performed before the 10th week, it will carry, among other things, a risk of limb defects. The incidence of limb defects is 5.7 per 10,000 cases, including minor nail defects, or 5.2 per 10,000 cases, if they are excluded [Kuliev et al., 1996]. The mean rate of spontaneous fetal loss due to chorionic biopsy is 2.5%. Compared to

second-trimester amniocentesis, chorionic biopsy is associated with more technical and sampling problems, more false-positive and false-negative results, and more spontaneous abortions (odds ratio: 1.33; 95% CI: 1.17 to 1.52) [Alfirevic et al., 2002].

Chorionic biopsy is the procedure recommended for first-trimester prenatal diagnosis, but studies on this are inconclusive. In Québec, it is performed only at two hospitals. The learning curve for this technique is long, and performing a large number of procedures is required in order to maintain competence. In addition, analyzing the chorion is more labor-intensive than analyzing amniocytes, and chorionic analysis cannot be performed systematically with the resources at Québec's cytogenetic laboratories (according to written information from Dr. Jacques Michaud, Service de génétique médicale, Hôpital Sainte-Justine, Montréal, Québec).

3.3 Techniques under development

3.3.1 Fetal cells in maternal blood

Since the 1970s, researchers have attempted to develop a technique for detecting fetal cells in maternal blood, in order to perform genetic tests on fetal DNA in those cells. A certain number of methods are currently available, and this technology could, in the years to come, compete with amniocentesis and chorionic biopsy and even replace them. Its main advantage is that it yields fetal cells, mainly nucleated erythrocytes, by a noninvasive technique (obtaining maternal blood from a peripheral vein), which does not require any special expertise on the part of the technician and which thus avoids all the risks for the mother and fetus. This technique is described later in this report.

3.3.2 Urinary markers

The measurement of different metabolites in maternal urine is still investigational. Study results show wide variability, and the clinical value of these markers still needs to be determined. A brief description is provided in Chapter 8.

3.4 Other related techniques

3.4.1 Dating ultrasound

Ultrasound is the most reliable method for estimating gestational age, this by measuring the biparietal diameter or crown-rump length [Wald et al., 1992; Wald et al., 1993]. The conventional method of calculation based on the date of the last period leads to an error of two weeks in 15% of cases [Haddow et al., 1994]. The accuracy of the gestational age calculation is important in interpreting the results of maternal serum screening. The accuracy of the calculation of the week of pregnancy during which the sample is obtained can reduce the number of pregnancies considered to be at high risk – which is why prenatal diagnosis is advised – by one half. Dating ultrasound should therefore be combined with serum marker assays.

3.5 Genetic counselling and information provided to couples

Prenatal screening is used to assess the risk of carrying an affected child and, if the risk is found to be high, provides the option of prenatal diagnosis. Prenatal diagnostic techniques pose certain risks to the mother and fetus, and, in cases where a fetus is diagnosed with Down syndrome or some other chromosome abnormality, the only available preventive measure is termination of pregnancy. A mother or

couple who agree to participate in prenatal screening should receive all the necessary information concerning the existence of two different risks, the risk of having a child with Down syndrome and the risk of losing an unaffected fetus as a result of diagnostic procedures. It should be checked that the parents understand the limitations of screening and the difference between screening and diagnosis. First-line information can be provided by health professionals who are not specialized in genetics and who are not necessarily physicians. More specialized information provided by genetic specialists or genetic counsellors should help parents interpret the results of the screening if it reveals a high risk and decide voluntarily whether or not to participate in prenatal diagnosis. Lastly, the genetic counsellor should support the parents in their decision to continue or terminate the pregnancy and inform them of the risks associated with future pregnancies [CETS, 1999].

4

FIRST-TRIMESTER SERUM MARKERS

A number of maternal serum markers have been investigated in order to determine their potential use, between the 10th and 14th week of pregnancy, in cases of singleton pregnancies. Some of these markers are also used in second-trimester prenatal Down syndrome screening [Wald et al., 1997]. The results of assays of these serum markers, which are expressed in multiples of the median (MoM), not in absolute values, are used to calculate a likelihood ratio. The ratio is then multiplied by the prevalence of Down syndrome for the mother's age to arrive at an estimate of the individual risk, expressed as 1/N, for each woman. The median is the value observed for serum markers in unaffected pregnancies of the same gestational age in the reference population.

Two markers seem to offer the most accuracy during the first trimester – PAPP-A and the free β-subunit of chorionic gonadotropin (β-hCG), both of which are measured between the 8th and 13th week of pregnancy, the ideal time being before the 12th week [Wheeler and Sinosich, 1998]. Adding other markers, such as inhibin-A, measured between 10 and 14 weeks' gestation, does not seem to improve the performance of Down syndrome screening [Spencer et al., 2001]. In this report, we have limited ourselves to reviewing studies that included PAPP-A and free β-subunit hCG measurements.

β-hCG values are almost twice as high (1.8 MoM) and PAPP-A values 50% lower (0.4 MoM) in Down syndrome fetuses compared to the values observed in unaffected singleton pregnancies. The efficacy of the PAPP-A measurement decreases after the 14th week, its median value being 0.9 MoM at that point and 1 MoM between the 17th and 19th week [Wald et al., 1996b]. The combination of these markers and maternal age yields a detection rate of 62%, with 5% false-positive results [Wald et al., 1997]. Other markers and different combinations have been investigated, but the results were even less accurate [Spencer et al., 2000a]. Down syndrome screening based on serum markers seems to have low sensitivity in twin pregnancies, although this has been investigated very little [Senat et al., 2001].

We reviewed the published studies that had examined the detection rate and false-positive rate for first-trimester Down syndrome screening based on PAPP-A and β-hCG measurements alone or in combination with maternal age. A description of these studies is presented in Table B-1 in Appendix B. The main results of the studies that combined the risk based on serum markers and maternal age are presented in Table 1. In Table 2, we indicate the anticipated detection rate calculated in different studies with serum marker measurements, and the risk associated with maternal age.

The detection rate observed by combining β-hCG and PAPP-A measurements and maternal age is between 56 and 67% (5% false-positive results). The estimated detection rate for a given population, based on a model using calculated efficacy data and the risk according to maternal age, is between 49 and 79%. These rates are relatively uniform, based on observations in various studies, and they compare with the performance obtained with two markers measured during the second trimester, although the efficacy is lower compared to the second-trimester triple and quadruple markers [Canick and Kellner, 1999].

Comparable results were obtained by Cuckle and van Lith by combining, in a meta-analysis, the results of 44 studies that had examined the performance of prenatal screening with different markers between the 9th and 11th week. The detection rate obtained with PAPP-A (18 studies) and β-hCG (17 studies) combined was 64.6%, with 5% false positives [Cuckle and van Lith, 1999].

However, a certain number of affected pregnancies end spontaneously between the first and second trimester. It is estimated that 43% of Down syndrome pregnancies end spontaneously in abortion or stillbirth between the chorionic biopsy (first trimester) and term. The figure is 23% between the amniocentesis (second trimester) and term [Morris et al., 1999]. Given these spontaneous fetal losses, the detection rate has to be at least 8.3% higher in order for the efficacy of first-trimester screening to be superior to that of second-trimester screening [Dunstan and Nix, 1998]. Berry et al. compared the proportion of pregnancies considered to be at high risk upon first-trimester screening with those at high risk identified during the second trimester. They compared the first-trimester measurements of free β-hCG and PAPP-A and the second-trimester measurements of AFP and hCG for 45 Down syndrome pregnancies.

Table 1

Detection rate, during the first trimester, obtained with serum markers (β-hCG and PAPP-A), for a 5% false-positive rate

Study	Population	Study design	Number of fetuses	Gestational age (weeks)	DS cases detected/ number of cases	Detection rate %	Cut-off
β-hCG and PAPP-A							
Casals et al., 1996[1]	At-risk	R	1,138	10-13	8/19	42	–
Krantz et al., 1996	–	R	505	10-13	15/22	68	1:255
Maternal age, β-hCG and PAPP-A							
Wald et al., 1996b*	At-risk	R	460	8-14	48/77	62	1:275
Forest et al., 1997*	Mixed	P	10,160	9-13	10/18	56	1:250
Berry et al., 1997	Mixed	P	10,600	< 15	27/45	60	1:270
Wheeler et al., 1998*	At-risk	R	713	9-12	11/17	67	–
Haddow et al., 1998*	At-risk	P	3,217	9-13	29/48	60	1:385
All studies			**25,150**		**125/205**	**61**	

(1) A detection rate of 82% (5% false positives) was obtained by combining AFP and PAPP-A.

*Multicentre study.

Design: Retrospective (R) or prospective (P).

DS: Down syndrome.

Mixed population: High- and low-risk pregnancies combined. Some studies involved an unselected population.

At-risk population: A population of pregnant women participating in prenatal diagnosis by amniocentesis or chorionic biopsy because of their high risk.

Table 2

Estimated first-trimester detection rate in a population that underwent screening using the serum markers β-hCG and PAPP-A combined with maternal age, for a 5% false-positive rate

Study	Study design	Number of fetuses	Gestational age (weeks)	Estimated detection rate % and (95% CI)
Brambati et al., 1994	R	102	8-12	78.9 (64.9-92.8)
Krantz et al., 1996	R	505	10-13	63
Berry et al., 1997	P	10,600	< 15	49 (34-62) 55 (41-70)[1]
Wheeler et al., 1998*	R	713	9-12	68.8
Tsukerman et al., 1999	R	1,595	9-13	69

Design: Retrospective (R) or prospective (P); CI: Confidence interval.
(1) β-hCG (MoM): PAPP-A (MoM) ratio combined with maternal age.
*Multicentre study.

Upon combining the risk obtained with that associated with maternal age, they detected, during the first trimester, 27 of the 45 cases (60%). Second-trimester screening detected 39 of the 45 cases, or 12 additional cases (87%) [Berry et al., 1997]. To our knowledge, there have been no other published controlled studies of the different first- and second-trimester prenatal maternal serum marker screening techniques.

Most of the published studies of first-trimester maternal serum screening were retrospective and involved high-risk women. Although the efficacy of first-trimester prenatal screening is relatively well established, its effectiveness has not been investigated. Certain factors make it difficult to calculate the detection rate and to assess its impact on the decrease in the prevalence of Down syndrome. First, it is possible that the detection rate is overestimated, since, when calculating it, spontaneous losses of Down syndrome fetuses are not always included in the denominator. This applies to second-trimester screening as well. Second, since most pregnancies diagnosed with an aneuploidy were terminated voluntarily, the relationship between first-trimester screening and spontaneous pregnancy terminations cannot be evaluated. If spontaneous abortions occur mainly during pregnancies considered to be at high risk, screening will have little impact on the birth prevalence of Down syndrome. Furthermore, if this assumption is correct, many pregnant women will be confronted with the choice of voluntarily terminating their pregnancy, even though it could terminate spontaneously. The repercussions of this have not been assessed. The same overestimation bias is present when the outcome of the pregnancy is not known in all cases and when certain cases of aneuploidy may not be included in the denominator for test performance calculations.

Estimating the risk with second-trimester maternal serum markers requires certain adjustments for maternal weight and smoking, parity, fetal sex, the presence of type 1 diabetes, if applicable, and the mother's ethnic origin. The effect of these factors on the calculation of second-trimester marker MoM is well documented, which is not the case for the first-trimester markers. However, in practice, the said adjustments are not always made. Spencer et al. examined the influence of ethnic origin in a population of 5,422 Caucasian women, 752 Afro-Caribbean women and 170 Asian women following first-trimester marker screening. The serum marker levels were significantly different between the groups, but the impact of the correction on the detection rate was relatively modest, namely, a 1.4% increase [Spencer et al., 2000b]. Maternal weight and smoking also have a significant influence on first-trimester marker levels, while gravidity, parity and fetal sex seem to have little influence [de Graaf et al., 2000]. A recent exploratory study revealed a significant correlation, during subsequent pregnancies, between the results of first-trimester biochemical marker screening. In a woman who is screen-positive for Down syndrome during her first pregnancy, the probability of having the same result during subsequent pregnancies is 1.5 to 2 times higher. This correlation had previously been observed during second-trimester screening. However, the same exploratory study showed that there is no such correlation between different pregnancies in a given woman with regard to nuchal translucency [Spencer, 2001].

First-trimester biochemical marker measurement can also detect 63% of cases of trisomy 18 [Orlandi et al., 1997], but it does not detect open neural tube defects. The serum hCG, β-hCG and PAPP-A concentrations were 0.31, 0.22 and 0.30 MoM, respectively, in pregnancies with trisomy 18 fetuses [Haddow et al., 1998]. The spontaneous abortion rate is 83% between the first trimester and term for trisomy 18 or 13 (Patau's syndrome) fetuses [Whitlow et al., 1999].

In summary, first trimester markers combined with maternal age can reportedly detect between 56 and 67% (61% on average) of Down syndrome cases, with 5% false positives. This performance seems comparable to that of second-trimester markers, even if a number of studies involved high-risk pregnant women and did not take the spontaneous loss of Down syndrome fetuses between the first and second trimester into account. The only study that has compared first-trimester and second-trimester maternal serum screening showed the latter to be superior. These results would need to be confirmed by larger studies. While they may be of equal performance, first-trimester screening permits an earlier diagnosis, but it has the disadvantage of providing an unnecessary diagnosis in a higher percentage of women whose pregnancies would terminate spontaneously before term.

5

FIRST-TRIMESTER ULTRASOUND

First-trimester ultrasound is a reliable method for estimating gestational age and permits the early detection and better management of multiple pregnancies. It also contributes to a better assessment of intrauterine growth problems. Prenatal ultrasound screening at the end of the first trimester consists in measuring nuchal translucency, that is, the subcutaneous space between the fetal cervical spine and the overlying skin. The reason for increased nuchal translucency in trisomic fetuses is still a subject of debate. It is apparently due to a certain amount of edema that forms at the back of the fetus' neck and which is promoted by its tendency to lie on its back and by the laxity of the skin on the neck. The edema is associated with a number of pathologies, including cardiac malformations and chromosome abnormalities [Berger, 1999]. In addition to the presence of edema, according to some hypotheses, increased nuchal translucency is caused by a metabolic abnormality with hypersecretion of mucopolysaccharides. Increased nuchal translucency is also associated with cystic hygroma, which is due to overdistention of jugular lymphatic sacs resulting from failed communication with the internal jugular vein, and it is often indicative of other congenital abnormalities [Stewart and Malone, 1999].

5.1 Efficacy of nuchal translucency measurement

Nuchal translucency is measured between the 10th and 14th week of gestation. When ≥ 3 mm or above the 95th or 99th percentile for the gestational age, it indicates a high risk of Down syndrome and of other aneuploidies and fetal malformations [Devine and Malone, 1999]. The definition of nuchal translucency is not uniform in the literature, which makes a synthesis of study results difficult. Depending on the study, the risk cut-off level used is between 2.5 and 4 mm. The use of a set cut-off level is not appropriate for normal pregnancies because of the physiological increase in nuchal translucency between the 9th and 14th week of pregnancy. Using a sliding cut-off level that varies according to the week of pregnancy improves screening performance and reduces the number of false-positive results [Faraut et al., 1999; Nicolaides et al., 1996; Pajkrt et al., 1995].

In twin pregnancies, nuchal translucency can be measured in each fetus. In dichorionic pregnancies, the risk is calculated for each fetus separately. For monochorionic pregnancies, there are presently no data for determining which of the two measurements should be used to assess the risk [Senat et al., 2001].

Nuchal translucency measurement requires a standardized technique that guarantees its repeatability. The measurement should be made when the fetus is in a sagittal position with the back of the neck in a neutral position, that is, when the angle between the sagittal spine and the occiput is equal to zero [Whitlow et al., 1998; Senat et al., 2001]. In a small number of cases, the examination cannot be performed or requires more time because of the fetal position not permitting a proper nuchal translucency measurement. In such cases, an examination at a later time is necessary. The equipment used must be of good quality and have a video-loop function and calipers capable of providing measurements to one decimal point, which means that each caliper movement must not exceed 0.1 mm [Mahieu-Caputo et al., 2002; Nicolaides et al., 2002]. The success rate and repeatability of nuchal translucency measurements are examined later in this report (Section 5.2).

A number of studies have examined the performance of nuchal translucency measurement in first-trimester aneuploidy screening. Some of them

give the detection rate and the false-positive rate but do not take the risk associated with maternal age into account (Table 3), while others combine the risk associated with maternal age and that associated with nuchal translucency thickness (Table 4). Those studies that present results for both of the described methods for calculating the risk, i.e., nuchal translucency alone or combined with maternal age, are presented in Table 4 only.

On average, the detection rate with nuchal translucency measurement was 66% in the studies involving a mixed or unselected population and 69% in those involving only high-risk women, i.e., those for whom an amniocentesis or a chorionic biopsy had been recommended because of a high risk. When the risk associated with nuchal translucency and that associated with maternal age are combined, the mean detection rate is 80%. However, it should be noted that the risk cut-off level and the false-positive rate differed from study to study.

In a recent review, Stewart and Malone revisit the problem of overestimating the detection rate when the calculation does not take spontaneous losses between the first trimester and term into account. For example, if the first-trimester prevalence of Down syndrome is calculated with data from a study by Snijders et al., the detection rate would be 60% instead of 82% (8.3% false positives) [Haddow, 1998; Snijders et al., 1998]. This observation is all the more relevant because Snijders et al. examined nuchal translucency in 96,127 fetuses in an unselected population at 22 centres in the United Kingdom. The 306 sonographers who took part in the study used uniform standards for their ultrasound evaluations and risk calculations [Stewart and Malone, 1999].

This would also explain why population studies aimed at verifying the repercussions of prenatal Down syndrome screening have shown that, despite a high detection rate and an equally high pregnancy determination rate, the prevalence of live births with Down syndrome only decreases slightly, probably because of the screening and diagnosis of an increasing number of cases that would end spontaneously between the time of diagnosis and term [Mutton et al., 1998; De Vigan et al., 1999]. In fact, the data presented by Mutton et al. show that, in England and Wales, the number of Down syndrome cases diagnosed prenatally increased from 321 in 1989 to 696 in 1997 (a 54% increase), but that the number of cases diagnosed after birth (including live births, stillbirths and neonatal deaths) decreased from 760 in 1989 to 640 in 1997 (a 16% decrease) [Mutton et al., 1998]. According to the Registre des anomalies congénitales de Paris data, 76.3% of the 670 Down syndrome cases were diagnosed prenatally between 1992 and 1997. The prevalence of Down syndrome births decreased from 9.0 to 7.7 per 10,000 births during that period [De Vigan et al., 1999].

Verifying pregnancy outcomes is another factor that influences the detection rate. Only a few studies provide these data in all cases [Kornman et al., 1996; Nicolaides et al., 1994; Taipale et al., 1997; Schwarzler et al., 1999]. In the others, the proportion varies from 83 to 98%, or the figure is not given. Most of the studies were of retrospective design and only reported the follow-up of fetuses with a nuchal translucency measurement above the chosen cut-off. The definition of this cut-off and the week of pregnancy during which the measurement was made varied from study to study.

Table 3

Down syndrome detection rate and false-positive rate for first-trimester nuchal translucency measurement

Study	Ultrasound	Number of fetuses	Week of gestation	NT (mm or percentile)	Detection rate Cases detected/number of cases (%)		FP
	Approach				Aneu-ploidies	DS	%
Mixed or unselected population							
Bewley et al., 1995	–	1,127	8-13	≥ 3	2/5 **(40)**	1/3 **(33)**	6
Hafner et al., 1995	TA	1,972	10-13	≥ 2.5	8/11 **(73)**	2/4 **(50)**	1.2
Szabo et al., 1995	TV	3,380	9-12	≥ 3	43/46 **(94)**	27/30 **(90)**	1.6
Kornman et al., 1996	TA	923	≤ 13	≥ 3	2/10 **(20)**	2/7 **(29)**	4
Taipale et al., 1997	TV	10,010	10-15.9	≥ 3	18/26 **(69)**	7/13 **(54)**	1
Thilaganathan et al., 1997	–	3,604	10-14	–	14/18 **(78)**	5/7 **(71)**	5
Hafner et al., 1998	–	4,233	10-13	≥ 2.5	11/17 **(65)**	3/7 **(43)**	1.7
Pajkrt et al., 1998b	TA	1,473	10-14	≥ 3	8/15 **(53)**	6/9 **(67)**	2.2
Whitlow et al., 1999*	TA + TV	6,443	$11\text{-}14^{+6}$	≥ 99th	31/40 **(78)**	15/23 **(65)**	1
All studies		**33,165**				**68/103 (66)**	
High-risk population							
Savoldelli et al., 1993	TA	1,400	9-12	≥ 4	19/43 **(44)**	15/28 **(54)**	0.4
Nicolaides et al., 1994	TA	1,273	$10\text{-}13^{+6}$	≥ 3	33/46 **(72)**	21/25 **(84)**	4.5
Brambati et al., 1995	TA + TV	1,819	8-15	≥ 3	13/43 **(30)**	–	4
Comas et al., 1995	TV	453	9-13	≥ 3	9/18 **(50)**	4/7 **(57)**	9.3
Pajkrt et al., 1998a**	TA	2,247	10-14	≥ 3	30/63 **(48)**	25/36 **(69)**	4
Acacio et al., 2001	TA/TV	230	10-14	≥ 2.5	16/23 **(70)**	9/12 **(75)**	12.5
All studies		**7,422**				**74/108 (69)**	

NT: Nuchal translucency; DS: Down syndrome; FP: False positives; –: Not specified; TA: Transabdominal ultrasound; TV: Transvaginal ultrasound; TA + TV: Transabdominal ultrasound and, if visualization was unsatisfactory, transvaginal ultrasound; TA/TV: Transabdominal or transvaginal ultrasound.

* 1,632 fetuses previously included in the study by Economides et al., 1998.

** Adjusting the measurement for variations due to gestational age does not improve performance.

Table 4

Detection and false-positive rates with first-trimester (10-14 weeks) nuchal translucency measurement combined with maternal age

Study	Ultrasound	Number of fetuses	Cut-off	Detection rate Cases detected /number of cases (%)		FP
	Approach			Aneuploidies	DS	%
MIXED OR UNSELECTED POPULATION						
Pandya et al., 1995b*	TA + TV	20,381	1:100	129/164 **(79)**	69/86 **(80)**	4.9
Snijders et al., 1998*	TA + TV	96,127	1:300§	521/651 **(80)**	268/326 **(82)**(1)	8.3
Theodoropoulos et al., 1998*	TA + TV	3,550	1:100 1:300	19/22 **(86)** 21/22 **(95)**	9/11 **(82)** 10/11 **(91)**	2.6 4.9
Pajkrt et al., 1998b	TA	1,473	1:100 1:300	9/15 **(60)** 13/15 **(87)**	7/9 **(78)** 9/9 **(100)**	7.6 19
Schwarzler et al., 1999	TA + TV	4,523	1:270	18/23 **(78)**	10/12 **(83)**	4.7
Thilaganathan et al., 1999	TA	11,398	1:200	40/49 **(81)**	16/21 **(76)**	4.7
Zoppi et al., 2000**	TA + TV	5,210	1:100 1:300	54/73 **(74)** 65/73 **(89)**	33/47 **(70)** 38/47 **(81)**	4.2 11.1
Brizot et al., 2001	TA + TV	2,996	1:100 1:300	18/22 **(82)** 18/22 **(82)**	9/10 **(90)** 9/10 **(90)**	3.1 7.4
Gasiorek-Wiens et al., 2001*	TA - TV	21,959	1:100 1:300	378/484 **(78)** 423/484 **(87)**	167/210 **(80)** 184/210 **(88)**	6 13
Michailidis et al., 2001	TA + TV	7,447	–	–	19/23 **(83)**	5
Zoppi et al., 2001	TA + TV	10,001	1:100 1:300	81/110 **(74)** 97/110 **(88)**	49/64 **(77)** 58/64 **(90)**	3 9
All studies		**185,065**			**656/819 (80)**¶	

DS: Down syndrome; FP: False positives; –: Not specified; TA: Transabdominal ultrasound; TV: Transvaginal ultrasound.

* Multicentre study.

** The time the measurement was made in this study was between 10 weeks 3 days and 13 weeks 6 days.

(1) The rate is 77% if the false-positive rate is set at 5%.

§ If the cut-off is NT > 95th percentile, the detection rate is 71% for aneuploidies and 72% for DS, with 4.4% false-positive results.

¶ This mean rate was calculated on the basis of a risk cut-off level of 1:100 in those studies in which more than one risk cut-off level is indicated.

The considerable differences in the detection and false-positive rates between the studies could mainly be explained by the diversity of the study populations, the lack of a uniform ultrasound technique, and differences in sonographer training, the quality control mechanisms, the ultrasound techniques used, the definition of the risk cut-off level, and the quality of the pregnancy outcome follow-up [Stewart and Malone, 1999]. In light of the observed differences between the studies, and stressing the potential for first-trimester nuchal translucency measurement as an early marker of Down syndrome, the authors question the applicability of first-trimester ultrasound screening performed outside tertiary-level medical centres.

The differences in the results obtained at the various centres are also evident in the study by Haddow et al., in which nuchal translucency was measured in 3,991 fetuses at high risk for Down syndrome at 16 prenatal diagnostic centres in the United States. The reported success rate is 83%, with a range of 61 to 100%, depending on the centre. The mean detection rate for the 16 centres, based on the nuchal translucency measurement above the 95th percentile for the week of gestation chosen by each centre, was 31%, with 5% false positives, but it was between 0 and 100% between the different centres [Haddow et al., 1998]. Standardizing the measurement and the quality control could permit better measurement repeatability and accuracy. In this regard, the Fetal Medicine Foundation instituted a quality control system which includes education that takes the sonographer's previous experience into account and a validation period of 50 examinations, with corrections and comments on each image. Next, a quarterly statistical analysis of the distribution of each sonographer's nuchal translucency measurements is performed to detect any deviations. If need be, an examination of randomly selected images enables the sonographer to correct his or her technique [Senat et al., 2001]. It should be noted that in most of the recent studies [Brizot et al., 2001; Gasiorek-Wiens et al., 2001; Zoppi et al., 2001], the sonographers held a Fetal Medicine Foundation certificate of competence. The detection rate in those studies was excellent, ranging from 77 to 90%, with 3 to 6% false-positive results. These experiences show that special training for sonographers and quality control play a key role in optimizing screening with this technique.

In addition to the limitations mentioned above, studies show differences in terms of the ultrasound technique used, be it transabdominal or transvaginal, and the time allotted to the examination, which varied or which was not reported. In the case of unselected populations, the performance of nuchal translucency measurement was superior when the transabdominal approach was used in combination with the transvaginal approach.

In summary, the aim of first-trimester (10th to 14th week) ultrasound is to measure nuchal translucency. Nuchal translucency ≥ 3 mm (between 2.5 and 4 mm, depending on the study) or above the 95th or 99th percentile for the gestational age indicates a high risk of Down syndrome or of other aneuploidies. The mean detection rate was 69% in studies involving high-risk populations and 66% in studies involving mixed or unselected populations. It was 80% if the nuchal translucency measurement was combined with maternal age in order to assess the risk in mixed or unselected populations. As is the case with serum markers, this rate could be lower if the prevalence of Down syndrome at term instead of its first-trimester prevalence were taken into account. The differences observed between the studies and between centres reflect problems when using nuchal

translucency measurement outside of tertiary centres or an experimental context or in the absence of specific training on this technique.

5.2 Nuchal translucency measurement: Success rate and repeatability

A large number of studies of the performance of nuchal translucency measurement report the success rate of this technique and the repeatability of this measurement. A neutral fetal position is an absolutely necessary condition for the accuracy of this measurement, and the time allotted to the examination, the sonographer's competence and the quality of the equipment can have an impact on the success rate and the measurement's repeatability.

Tables 5 and 6 indicate the success rate and the repeatability coefficient obtained in different studies, together with the ultrasound techniques used and the amount of time allotted to the examination.

Table 5
Success rate of the nuchal translucency measurement

Study	Time allotted to examination	Week of gestation	Ultrasound	Success rate (%)
Hafner et al., 1995	–	10-13	TA	100
Braithwaite et al., 1995	20 minutes	12-13	TA TV TA + TV	92 90 100
Pandya et al., 1995b	–	10-14	TA + TV	100
Kornman et al., 1996	3 additional minutes	< 10-14	TA	58
Pajkrt et al., 1998a	No limit	10-14	TA	98
Pajkrt et al., 1998b	No limit	10-14	TA	96
Whitlow et al., 1998	30 minutes Most: 10 minutes	10-14 –	TA TA + TV	82 97
Theodoropoulos et al., 1998	–	10-14	TA + TV	100
Kurjak et al., 1999	15-20 minutes 3-5 minutes	10-14	2-D TV 3-D TV	85 100
Thilaganathan et al., 1999	–	10-14	TA	90
Chung et al., 2000	Average of 5 minutes	$10\text{-}14^{+6}$	3-D TV	100
Gasiorek-Wiens et al., 2001	–	10-14	TA + TV	100
Zoppi et al., 2001	–	10-14	TA + TV	100

TA: Transabdominal ultrasound; TV: Transvaginal ultrasound; –: Not specified.

Table 6
Repeatability coefficient for nuchal translucency measurement

Study	Time allotted to examination	Week of pregnancy	Ultrasound	Repeatability coefficient
Pandya et al., 1995a	–	10-14	TA	0.54 mm (intraoperator) 0.62 mm (interoperator) 0.58 mm (intercaliper)
Braithwaite et al., 1995	20 minutes 20 minutes	12-13	TA TV	0.40 mm 0.22 mm
Taipale et al., 1997	–	10-15.9	TV	0-0.25 mm (intraoperator) 0-0.3 mm (interoperator)
Whitlow et al., 1998	20 minutes	11^{+2}-14^{+5}	TA	0.48 mm (neutral) 0.70 mm (flexed) 1.04 mm (extended)
Schwärzler et al., 1999	–	10-14	TA + TV	0.35 mm (intraoperator) 0.38 mm (interoperator)

TA : Transabdominal ultrasound; TV: Transvaginal ultrasound; –: Not specified.

Excluding the study by Kornman et al., the success rate varied from 82 to 100%. Adekunle et al. indicate that for 846 (15%) of the 5,821 pregnancies included in their study, nuchal translucency was not measured, either because it was not possible to do so or because the examination was declined [Adekunle et al., 1999].

In some studies, the amount of time allotted to measuring nuchal translucency was limited, while in others, the sonographers could take the time needed to obtain a measurement. In the study by Kornman et al., for example, three additional minutes was allotted for measuring nuchal translucency, which was the shortest measuring time in all the studies identified that used transabdominal ultrasound. It is interesting to note that the success and detection rates in their study, 58% and 29%, respectively [Kornman et al., 1996], are the lowest rates reported.

Chung et al. calculated the success rate and the intraoperator variations by measuring nuchal translucency with a three-dimensional vaginal technique in 86 fetuses between 10 weeks and 14^{+6} weeks of pregnancy. A satisfactory measurement was obtained in all cases. Intraoperator variation was determined with two measurements in all fetuses. The mean difference between the two measurements was 0.002 mm $\pm$ 0.124 mm ($p = 0.862$) [Chung et al., 2000].

Some studies have calculated an intraoperator, interoperator or intercaliper repeatability coefficient for nuchal translucency measurement (Table 6). A repeatability coefficient of 0.40 mm means that, if a TA ultrasound nuchal translucency measurement is 2.2 mm, the actual value can vary from 1.8 mm to 2.6 mm. These differences have major repercussions on the risk calculation. For example, for a 29-year-old

woman, a nuchal translucency of 2.2 mm corresponds to a risk of 1:1,853, but a nuchal translucency of 2.6 mm corresponds to a risk of 1:122 [Braithwaite et al., 1995].

Roberts et al. observed poor nuchal translucency measurement repeatability. In their study, 9 of the 48 cases examined (18.8%) were reallocated to a different risk group after a second measurement made by a different sonographer. Thirty measurements showed a difference of 1 mm and four a difference of 2 mm. After a second measurement made by the same sonographer, 15 of the 86 cases examined (17.5%) were reallocated, and 27 measurements showed a difference of 1 mm. After the second assessment of a freeze-frame, 16 of the 129 cases (12.4%) were reallocated and 31 measurements showed a difference of 1 mm [Roberts et al., 1995].

In summary, nuchal translucency was measured satisfactorily in 82 to 100% of cases. The success rate was 58% in one study in which only 3 additional minutes was allotted for this measurement. The success rate was higher in those studies where transvaginal ultrasound was performed after an unsatisfactory nuchal translucency measurement obtained transabdominally. It was 100% when a three-dimensional transvaginal technique was used. The repeatability coefficient varied from 0.22 mm to 1.04 mm in the studies, and these differences had major repercussions on the risk calculation. Most studies of the performance of nuchal translucency measurement do not report the measurement repeat rate.

5.3 Role of nuchal translucency measurement in screening for other fetal pathologies

In most cases, increased first-trimester nuchal translucency (≥ 3.5 to 4 mm) is associated with fetal problems, regardless of the karyotyping results [Cha'Ban et al., 1996; Bilardo et al., 1998; Brady et al., 1998; Adekunle et al., 1999; Senat et al., 2002]. The results of the studies that have examined this are summarized in Table 7. The prevalence of fetal abnormalities in the population is relatively low, and although it seems to increase when the nuchal translucency measurement increases, no definite conclusions can yet be drawn [Souka et al., 1998].

In addition, increased nuchal translucency may also be associated with a higher risk of spontaneous abortion (2.9% vs. 1.7%) [Bewley et al., 1995]. Pajkrt et al. examined the relationship between nuchal translucency measurements and pregnancy outcomes in 2,088 karyotypically normal fetuses with no structural malformations. The results show that the likelihood ratio for spontaneous abortions increases as nuchal translucency increases. For nuchal translucency measurements under 3 mm, the ratio is 1.2. Between 3.0 and 3.9 mm, it is 3.1, and when the measurement is 4 mm or more, the ratio is 6.8. Most of the spontaneous abortions occurred in the group of fetuses with a nuchal translucency of 3 mm or more. To explain these findings, the authors postulate that increased nuchal translucency would potentially identify chromosomally normal fetuses, but also indicate a higher probability of dying in utero because of heart defects. The spontaneous abortion of these fetuses is due to cardiac anomalies, not to the diagnostic procedure (amniocentesis or chorionic biopsy). Furthermore, increased nuchal translucency may be indicative of hemodynamic instability due to temporary cardiac decompensation. In such cases, the fetus cannot withstand the strain of diagnostic procedures [Pajkrt et al., 1999].

Hyett et al. examined the utility of measuring nuchal translucency between the 10th and 14th week of gestation in screening for cardiac defects. Nuchal translucency was measured by transabdominal ultrasound, followed by transvaginal ultrasound if the

measurement could not be made transabdominally. The outcomes of the 31,162 singleton pregnancies were determined from a computerized database. Three hundred and twenty-three pregnancies in which a chromosome abnormality had been detected, 317 cases of spontaneous abortion and 1,368 pregnancies for which there were no outcome data were excluded from the sensitivity and specificity calculations. It was found that 56% of the major cardiac defects were associated with a nuchal translucency measurement above the 95th percentile [Hyett et al., 1999]. It should be noted that the cost of screening could increase substantially if all fetuses with a normal karyotype but with increased nuchal

Table 7
Follow-up of fetuses with a normal karyotype but with increased nuchal translucency

Study	Duration of follow-up	Number of fetuses with a nuchal translucency > 3.5 mm		
	Number of months	Karyotype		Normal karyotype
		Abnormal	Normal	
Cha'Ban et al., 1996	4-32	26/54 (48%)	28/54 (52%)	Live births, normal physical and mental development: 19/28 (68%) Malformations detected prenatally: 7/28 (25%) Fetal losses: 2/28 (7%)
Bilardo et al., 1998	–	25/74 (34%)	49/74 (66%)	Live births with no abnormalities: 32/49 (65%) Various abnormalities: 11/49 (22%) Abortions, stillbirths and neonatal deaths: 6/49 (12%)
Brady et al., 1998	6-42	–	90	Major abnormalities: 9/90 (10%) Minor abnormalities: 14/90 (16%) Lost to follow-up: 1/90 (1%)
Adekunle et al., 1999	12-38	15/53 (28%)	38/53 (72%)	Live births with no abnormalities: 16/38 (42%) Live births, malformations detected prenatally: 7/38 (18%) Fetal losses: 7/38 (18%) Lost to follow-up: 8/38 (21%)
Senat et al., 2002	12-72	71/160 (44%)	89/160 (56%)	Live births with no abnormalities: 48/89 (54%) Live births with defects detected prenatally: 6/89 (7%) Defects diagnosed at birth: 4/89 (4%) Delayed neurological development: 4/89 (4%) Minor orthopedic problems: 2/89 (2%) Fetal losses: 17/89 (19%) Lost to follow-up: 8/89 (9%)

translucency were subsequently subjected to more specialized examinations, such as fetal echocardiography. To date, only one study has been published on the diagnostic utility of transvaginal echocardiography in fetuses with a nuchal translucency measurement above the 95th percentile. In that study, the investigators obtained a sensitivity of 88% and a specificity of 97% for diagnosing cardiac malformations [Haak et al., 2002].

In summary, increased nuchal translucency in a karyotypically normal fetus could point to the presence of other fetal malformations or pathologies, especially cardiac malformations. In addition, the risk of spontaneous abortion in karyotypically normal fetuses increases proportionately with the increase in nuchal translucency.

6

THE COMBINED TEST: COMBINING FIRST-TRIMESTER SERUM AND ULTRASOUND MARKERS

Combining first-trimester serum and ultrasound markers may appreciably increase the performance of early screening for Down syndrome and other aneuploidies [Stewart and Malone, 1999]. We reviewed the prospective and retrospective studies that had examined the detection and false-positive rates of combined screening, i.e., serum marker assays and nuchal translucency measurement during the first trimester. These studies are summarized in Table B-3 (Appendix B).

The results obtained in the prospective and retrospective studies are presented in Tables 8 and 9, respectively.

The studies involved different populations in terms of the risk of Down syndrome and other aneuploidies. Only one study provides a detailed account of the pregnancy outcomes [Benattar et al., 1999] and two others the adjustment of the detection rate for spontaneous fetal losses between the first trimester and term [Biagiotti et al., 1998; Krantz et al., 2000]. They report the detection rate with nuchal translucency measurement and PAPP-A and β-hCG assays, and with maternal age [Orlandi et al., 1997; Di Biasio et al., 1999; De Graaf et al., 1999] or the detection rate estimated in a given population based on measurements and the birth distribution by maternal age [Orlandi et al., 1997; Wald and Hackshaw, 1997; Biagiotti et al., 1998; Benattar et al., 1999; Spencer et al., 1999; Krantz et al., 2000]. Two prospective studies combined nuchal translucency, the free β-hCG level and maternal age [Noble et al., 1996; Scott et al., 1996]. In their study, Noble et al. excluded the cases of spontaneous abortion (n = 10) and termination of pregnancy following a diagnosis of fetal malformation (n = 14). The nuchal translucency measurement data are from a study published by Brizot et al. in 1995 [Noble et al., 1996]. The study published by Scott et al., in 1996, makes no mention of the exclusions or cases lost to follow-up. Despite these methodological differences, the detection rate varied between 85 and 100%, for a false-positive rate of 3.3 to 14% in the prospective studies and between 76 and 89% (false-positive rate: 5%) in the retrospective studies.

Krantz et al. used a dried-blood-on filter-paper technique to determine serum marker levels. All the cases of trisomy 18 were detected (13/13). The authors give the detection rate adjusted for spontaneous fetal losses. In addition, they downplayed the overestimation bias introduced by the fact that they were unable to ascertain all the live-born cases of Down syndrome, since the number of cases identified at birth was the expected number [Krantz et al., 2000]. The use of filter paper is of particular interest in organizing a screening program, since transporting fresh specimens can affect the serum marker levels and increase the false-positive rate [Massé et al., 2000]. However, the use of specimens of dried blood on filter paper increases the inaccuracy of the marker assay results and therefore decreases, theoretically, screening performance. For now, the use of this technique is limited to mass screenings where a high level of inaccuracy can be tolerated, such as neonatal screening for phenylketonuria. Screening accuracy should always be verified by means of a comparison with conventional techniques [O'Broin et al., 1995; Adam et al., 2000].

In their retrospective study, which was published in 1998, Biagiotti et al. estimated the detection rate to be 75.8%. They also calculated that, if all the affected fetuses destined to miscarry (44%) could be identified by first-trimester screening, the expected detection rate would be 57% [Biagiotti et al., 1998].

Tableau 8

Prospective studies determining the detection and false-positive rates of combined first-trimester serum and ultrasound markers in Down syndrome screening

Study	Cut-off	Number of fetuses	Week of gestation	Test	Detection rate Cases detected/ number of cases (%)	FP (%)
Mixed or unselected population						
Benattar et al., 1999	1:250	1,656	12-14	TA ultrasound AFP, free β-hCG Maternal age	5/5 **(100)***	9.7
De Biasio et al., 1999**	1:350	1,467	10-13^{+6}	TA ultrasound PAPP-A, free β-hCG Maternal age	11/13 **(85)**	3.3
Krantz et al., 2000	1:270	5,809	10^{+4}-13^{+6}	Ultrasound¶ PAPP-A, free β-hCG Maternal age	**(91)** **(70)**	5 1.4
High-risk population						
Noble et al., 1996	–	2,561	10-13	TA ultrasound Free β-hCG Maternal age	**(85)**	5
Scott et al., 1996	1:250	302	10-13	TA ultrasound Free β-hCG Maternal age	**(87.5)**	14
Orlandi et al., 1997	1:380	744†	9-13^{+4}	TA ultrasound PAPP-A, free β-hCG Maternal age	**(87)**	5

FP: False positives; TA: Transabdominal ultrasound; TV: Transvaginal ultrasound.

* Aneuploidies: Detection rate: 100% (7/7).

** A diagnostic procedure was recommended to 704 women (48%) because of their advanced age.

¶ As per the Fetal Medicine Foundation protocol and performed by an FMF-trained sonographer.

† 2,010 pregnant women participated in the study, but only 744 underwent an ultrasound examination.

Wald and Hackshaw combined data from the following three studies: 1) nuchal translucency measurement in 86 Down syndrome fetuses [Pandya et al., 1995b]; 2) PAPP-A and β-hCG assays in 77 Down syndrome fetuses and 385 unaffected fetuses [Wald et al., 1996b]; and 3) nuchal translucency measurement in 561 non-Down syndrome fetuses [Schuchter et al., 1997]. They obtained a detection rate of 80%

(5% false positives) upon combining maternal age, nuchal translucency and serum markers and after adjusting the detection rate in each study for spontaneous fetal losses between the first trimester and term [Wald and Hackshaw, 1997]. However, the authors indicate that the association between the markers and spontaneous fetal loss still needs to be clarified.

The study by Spencer et al. provides the results obtained at a multidisciplinary prenatal screening clinic where all the procedures were performed and the risk estimated during a one-hour visit (one-stop clinic) between the beginning of June 1998 and the end of May 1999. Apart from the results provided in Table 9, it is interesting to note that 97.6% (4,088/4,190) of the women accepted first-trimester screening. In addition, 6.1% (257/4,088) of the women presented to the clinic too late for first-trimester screening and underwent second-trimester screening. As well, 91 women had been referred by other hospitals after the 14th week of pregnancy. In all, 348 women (8%) underwent second-trimester screening [Spencer et al., 2000c].

Zimmermann et al. calculated the detection rate for chromosome abnormalities in 1,151 pregnancies, including 23 cases of aneuploidy, 4 of which were Down syndrome cases. The detection rate with PAPP-A and nuchal translucency was 39% (FP = 2%) [Zimmermann et al., 1996].

Table 9

Retrospective studies determining the detection and false-positive rates for combined first-trimester serum and ultrasound markers in aneuploidies and Down syndrome screening

Study	Number of fetuses	Week of gestation	Test	Detection rate (%)	FP (%)
Wald and Hackshaw, 1997	–	10-14	TA ultrasound Free β-hCG, PAPP-A Maternal age	80	5
Biagiotti et al., 1998	232	10-13	TA ultrasound Free β-hCG, PAPP-A Maternal age	75.8	5
De Graaf et al., 1999	292	9-15	TA ultrasound Free β-hCG, PAPP-A	82	5
Spencer et al., 1999	1,156	10-14	Ultrasound Free β-hCG, PAPP-A Maternal age	89 70	5 1
Spencer et al., 2000c	4,190	10^{+3}-13^{+6}	Ultrasound Free β-hCG, PAPP-A Maternal age	86 (DS) 100 (T18/13)	6.7

DS: Down syndrome; T18/13: Trisomies 18 and 13; TA: Transabdominal ultrasound.

Rozenberg et al. very recently published the results of a prospective, multicentre French study of the combination of nuchal translucency measurement between the 12th and 14th week of pregnancy and maternal serum markers between the 14th and 17th week. Close to 9,500 women took part in the study. Of them, 5,506 underwent both screening modalities. The results of this study show that combining both modalities yields a detection rate of 80%, with 5% false positives [Rozenberg et al., 2002]. Another prospective, multicentre study, the FASTER Trial (First and Second Trimester Evaluation of Risk for aneuploidy), is currently under way in the United States. Some 62,000 women participating in the study will undergo first- and second-trimester prenatal screening for the purpose of comparing the two modalities in terms of efficacy. The first-trimester screening (10-14 weeks) is based on nuchal translucency combined with maternal age and serum PAPP-A and β-hCG levels. The second-trimester screening is performed after 15 to 18 weeks' gestation using the quadruple marker (AFP, uE3, hCG and inhibin-A)[2]. Patients were still being recruited for the FASTER Trial in 2002. The Serum, Urine and Ultrasound Screening Study (SURUSS) is currently underway in Europe. Its goal is to evaluate the efficacy, safety and efficiency of first- and second-trimester serum, urinary and ultrasound markers as well as their potential combination [Stewart and Malone, 1999]. Until the results of these studies become available, the combination of first-trimester serum and ultrasound markers should be considered experimental [Alton et al., 2001; Stewart and Malone, 1999].

In summary, the published literature on combined first-trimester serum and ultrasound markers reports detection rates of 76 to 100%. However, at such rates, this combined method does not result in a lower false-positive rate. At a detection rate of 70%, one can reportedly obtain a 1% false-positive rate. However, the detection rate could be lower if the outcome of the pregnancy were known in all cases and if spontaneous abortions were included in the calculation. Two prospective, multicentre studies are currently under way in the United States and in Europe to compare, among other things, the performance of first-trimester screening with that of second-trimester screening.

2. Data on the FASTER project are available at: http://www.firsttrimester.org/ (Page consulted on February 28, 2002).

7

THE INTEGRATED TEST (FIRST AND SECOND TRIMESTER OF PREGNANCY)

Because of the uncertainty as to the screening modality to be preferred and as to when it is best to use it during pregnancy, and because of the high false-positive rate, Wald et al. proposed a method integrating first- and second-trimester screening results. The method consists in combining the risk determined by first-trimester screening (serum and ultrasound markers) and that determined during the second trimester (serum markers) [Wald et al., 1999]. According to Cuckle, there are several ways to integrate different screening methods. One consists in making all the measurements, without disclosing the results until all the tests have been performed and the risk calculated. Another option is the sequential approach, in which the result of each test is disclosed as it becomes available and where the next test is performed only if the present one indicates a high risk. The sequential method used during the first and second trimesters is less efficient, but it does avoid the problem of waiting and permits immediate reassurance of the patient or enables her to decide whether to terminate the pregnancy earlier [Cuckle, 2001]. A number of centres are using a variant of the sequential method. It consists of second-trimester screening for all women who have not had first-trimester prenatal diagnosis because they were considered to be in a low-risk group after screening, not deliberately, but rather as a result of the fact that the ultrasound and serum tests were performed by different institutions in an uncoordinated fashion. Consequently, the women obtain two independent results, but the second-trimester risk calculation is incorrect, since the low risk calculated during the first trimester is not taken into account. Since this approach overestimates the risk as determined during the second trimester and therefore considerably increases the number of false positives [Hackshaw and Wald, 2000b], it should be banned. Adding a second or third test in the case of women with a borderline calculated risk reduces the false-positive rate, although it does not improve the detection rate very much [Cuckle, 2001].

Hackshaw and Wald examined the potential advantages of reporting partial results during combined and integrated tests. When the combined or integrated test is being considered, it should be asked whether the risk calculated from the nuchal translucency measurement and maternal age only is high enough to remain unchanged, regardless of the serum marker levels. The advantage of this approach is the possibility of giving a pregnant woman a result immediately after a nuchal translucency measurement and thus sparing her the unpleasantness of one or two blood samples. Similarly, at centres which offer the integrated test, there are questions as to whether a partial result based solely on first-trimester screening can indicate a high enough risk that would remain high, regardless of the second-trimester screening results [Hackshaw and Wald, 2001a].

They used published data on 480 affected pregnancies and 96,839 unaffected pregnancies. The integrated test proved to be more accurate, with 0.8% false-positive results, for a detection rate of 85% compared to 18.2% false positives for nuchal translucency measurement alone and 4.9% for the combined test (first trimester only). In the case of integrated screening, only 0.69 in 1,000 screened women would show a risk greater than 1 in 2 based on nuchal translucency, maternal age and the PAPP-A level (first trimester), and they would remain screen-positive after second-trimester screening with the quadruple marker (AFP, uE3, total hCG and inhibin-A). Partial reporting of the estimated risk is not beneficial. Furthermore, since it is difficult to report results only in high-risk cases, most women will have to consider two risks during their pregnancies, which causes confusion and dissatisfaction. Similarly, the

use of a second test when the first test is negative would lead to an incorrect risk estimate, unless the calculation is corrected for fetuses identified during the previous test [Hackshaw and Wald, 2001a].

The detection rate estimated by Wald et al. is 85%, but with a false-positive rate of 0.9%, which decreases considerably the number of amniocentesis and the accompanying risk of iatrogenic fetal loss. This was a "theoretical" study, in which the performance of the different markers was combined in mathematical models in order to "estimate" the performance that could be obtained theoretically. The performance of the integrated test is based on the assumption that there is no correlation between the first- and second-trimester markers [Wald et al., 1999]. De Biasio et al. examined the correlation between the first- and second-trimester serum markers but did not find any significant results, except for a positive correlation between first-trimester free β-hCG and second-trimester hCG [De Biasio et al., 2000].

Herman et al. examined the overlapping and degree of correlation between first-trimester nuchal translucency and second-trimester triple test results in 508 singleton pregnancies considered to be at low risk for aneuploidies, but they did not find a significant correlation. The two tests are complementary, and further studies are needed to find the most effective method of combining them in order to minimize the false-positive rate [Herman et al., 2000].

Michailidis et al. evaluated the efficacy of prenatal Down syndrome screening by first-trimester ultrasound followed by the second-trimester measurement of serum markers in a retrospective study involving 7,447 unselected pregnant women, 4,864 of whom underwent second-trimester marker screening. The second-trimester serum marker screening identified half of the Down syndrome fetuses that had not been detected during the first trimester, but the prevalence of affected fetuses was very low during the second trimester because of the previous screening [Michailidis et al., 2001].

A demonstration project of the efficacy of the integrated test (first and second trimesters) is currently under way in two Ontario hospitals. The results of the initial evaluation indicate a false-positive rate of 2% for Down syndrome and 2% for open neural tube defects. Pregnant women who give birth at these two hospitals are invited to participate in integrated-test screening instead of the second-trimester serum marker screening offered in Ontario. The integrated test includes a serum PAPP-A measurement and a nuchal translucency measurement during the first trimester (between the 10th and 14th week) and the triple test (AFP, estriol and hCG) during the second trimester (between the 15th and 18th week). The pregnant woman is informed of the screening results only after the triple test [Summers et al., 2000; Prenatal Screening Programs in Ontario, 2001]. The FASTER Trial and the SURUSS study will also provide data on the efficacy of integrating the first- and second-trimester tests and will shed light on the advantages of a sequential approach, if any.

In summary, the integrated test (first and second trimester of pregnancy), i.e. the first-trimester measurement of serum markers and nuchal translucency and the second-trimester measurement of serum markers, identifies 85% of Down syndrome cases, with fewer than 1% false-positive results. Since it includes an AFP measurement, the integrated test can also be used to screen for open neural tube defects. Apart from the technical performance, it should be stressed that integrated screening extends over five weeks, which is a long, anxiety-producing period of time for pregnant women. Disclosing results

gradually avoids the problem of having to wait a long time for them and immediately reassures the woman or enables her to decide whether to terminate the pregnancy earlier, but this method is less effective. For one thing, interpreting each component independently can cause a substantial increase in the false-positive rate. Second, if women whose risk was calculated during the first trimester undergo second-trimester screening, the second-trimester risk calculation must take the first-trimester screening results into account. If the first test had a high detection rate, the number of fetuses that remain to be identified by subsequent tests will be low, making such tests inefficient.

8

URINARY METABOLITES

The concentration of chorionic gonadotropin and its subunits and metabolites also increases in maternal urine in pregnancies with Down syndrome fetuses. The β-core fragment of this hormone and urinary estriol have been investigated as second-trimester urinary markers alone or in combination with serum or ultrasound markers [Bahado-Singh et al., 1998; Bahado-Singh et al., 1999a; Bahado-Singh et al., 1999b; Bahado-Singh et al., 1999c; Cole et al., 1999a; Cuckle et al., 1999; Hsu et al., 1999]. These techniques might have a sensitivity comparable to that of the second-trimester serum markers, but they are still in the experimental stage.

Cole et al. examined screening based on the measurement of urine hyperglycosylated hCG and total urine hCG between the 11th and 22nd week of pregnancy. They obtained a Down syndrome detection rate of 79%, with 5% false positives. The authors emphasize the value of a high-performance test that can be used during the first two trimesters of pregnancy and the advantages of obtaining a urine specimen over serum tests. On the other hand, this test cannot be used to measure AFP during the first or second trimester [Cole et al., 1999b]. A follow-up study, the SURUSS trial (Serum, Urine and Ultrasound Screening Study), is currently under way in Europe. The first-trimester screening results are blinded and are not used in clinical practice [Stewart and Malone, 1999]. The results will allow, among other things, to determine the efficacy of urinary markers. This promising technique is still investigational, since study results show wide variability and since its clinical value has yet to be determined [Canick et al., 1999].

9

FETAL CELLS IN MATERNAL BLOOD

The uncertainty of prenatal screening and the risks inherent in the diagnostic techniques have led to the development of more reliable and less invasive screening and diagnostic methods. One of them consists in searching for fetal cells in maternal blood. The information provided in this section is not based on an exhaustive review of the published literature. Rather, we report here the results of the latest studies on this subject.

There are some prerequisites for using fetal cells circulating in maternal blood for prenatal diagnostic purposes. First, there must be enough of them in order for one to obtain unambiguous test results. Second, the fetal cells must come from the current pregnancy, since the presence of cells from previous pregnancies can alter the results. Lastly, the fetal cells must be present in the blood of all pregnant women or of a sufficiently large percentage of pregnant women to justify the use of this test [Wachtel et al., 2001].

Several types of fetal cells (trophoblasts, lymphocytes, granulocytes and erythroblasts) are present in maternal blood during pregnancy, but their small numbers and fragility make their recovery and identification difficult [Bianchi, 1999]. Their presence in maternal blood is higher in cases of aneuploid fetuses and in cases of future preeclampsia. Because of the placental origin of trophoblasts, they have a 1% incidence of mosaics and are therefore not very useful in prenatal diagnosis [Bianchi, 1999]. The most promising blood cells seem to be nucleated erythrocytes (erythroblasts). They have a relatively short lifespan (90 days), and their concentration in maternal blood is very low [Bianchi, 1999], but there are six times as many of them in pregnancies with Down syndrome fetuses [Parano et al., 2001]. The ratio of fetal nucleated erythrocytes to nucleated maternal blood cells is $1:1 \times 10^7$ to $1:1 \times 10^8$. Fetal nucleated erythrocytes appear in maternal blood around the 10th week of gestation, thus permitting first-trimester prenatal diagnosis [Bianchi, 1999].

A recently published study showed that it is possible to repeatedly identify an extremely small number of fetal cells among millions of maternal cells. The researchers were able to identify between 2 and 6 fetal cells per millilitre of peripheral maternal blood between the 18th and 22nd week of pregnancy in 12 pregnant women aged 23 to 33 carrying a karyotypically normal male fetus. The fetal cells identified by a FISH technique were probably nucleated erythrocytes, trophoblasts and lymphocytes. Once identified, these cells can be subjected to cytogenetic molecular analysis and thus make it possible to diagnose aneuploidies [Krabchi et al., 2001].

Al-Mufti et al. published the results of a study that examined the role of FISH performed on maternal blood enriched for fetal cells by triple-density centrifugation and MACS (magnetic activated cell sorting) in the prenatal screening and diagnosis of fetal aneuploidies. The study involved 230 women in their 10th to 14th week of pregnancy with a singleton fetus who had been advised to undergo prenatal diagnosis because of advanced maternal age or a high risk detected by nuchal translucency measurement. Cells containing positive fetal hemoglobin were found in 222 women (97%), and in 142 of them, the fetal karyotype was normal. Karyotyping confirmed Down syndrome in 36 cases, trisomy 18 in 24 cases and trisomy 13 in 10 cases. With a cut-off of three-signal nuclei in 5% of the fetal cells, the use of FISH on maternal blood enriched for fetal cells could potentially identify 60% of Down syndrome fetuses, with a 0% false-positive rate. A cut-off of 3% could yield 97% sensitivity, with a 13% false-positive rate. When used as a screening technique combined with maternal age and nuchal translucency measurement,

this method could potentially detect 80% of cases, with a 1% false-positive rate [Al-Mufti et al., 1999].

Another approach is based on the detection of circulating extracellular fetal DNA in maternal blood by PCR (polymerase chain reaction). In 2000, Zhong et al. published the results of a study confirming the results of previous studies, namely, that the quantity of fetal DNA in maternal plasma is significantly higher in pregnancies in which the fetus has an aneuploidy, particularly Down syndrome. It was a retrospective study involving the analysis of plasma samples from 58 women with a mean gestational age of 14^{+4} weeks, 29 of whom had been carrying an aneuploid male fetus, the other 29 a euploid male fetus. The level of circulating DNA in the pregnancies with Down syndrome fetuses (15 cases) was twice that in the pregnancies with euploid fetuses. The DNA level was also increased in the cases of trisomy 13 (3 cases) and other chromosome abnormalities (4 cases), but not in the cases of trisomy 18 (6 cases). However, the number of cases was too small to confirm these findings [Zhong et al., 2000]. Compared to analyzing fetal cells in maternal blood, which requires procedures for enriching maternal blood for these cells, plasma DNA analysis has the advantage of being quick, robust and easy to perform on a large number of samples. Presently, the main limitation is the non-availability of unique fetal gene sequences, other than those associated with the Y chromosome, that could be used to identify the presence of fetal DNA from both male and female fetuses [Pertl and Bianchi, 2001].

These techniques are still investigational, but they could be used not only for the prenatal diagnosis of diseases in the fetus, but also for detecting certain diseases in the mother during pregnancy, such as preeclampsia, or after pregnancy, such as autoimmune diseases [Bianchi, 2000].

10

WOMEN'S PERSPECTIVE ON PRENATAL SCREENING

In this chapter, we only present the results of a few studies concerning women's perspective on prenatal screening. It is therefore not an exhaustive review of published studies.

10.1 Preference for first-trimester or second-trimester screening

Kornman et al. studied women's opinions of the advantages of first-trimester screening over second-trimester screening by means of a survey conducted among 181 pregnant women who were being followed at a prenatal care clinic and who had the option of participating in second-trimester maternal serum screening and among 96 pregnant women referred to a prenatal diagnosis clinic because of their age or history. The women who agreed to second-trimester screening (69%) would have preferred first-trimester screening had they had the choice. However, those who declined second-trimester screening (31%) would have declined first-trimester screening as well, their objections in this regard being the same for both time frames. The advantages ascribed to first-trimester screening were a shorter period of uncertainty, the option of terminating the pregnancy before fetal movements can be perceived and before the pregnancy is evident, and the lower risk of complications associated with early termination of pregnancy. A third of the women who had been advised to undergo prenatal diagnosis would have preferred first-trimester screening had they been given the choice, for the same reasons as those mentioned above [Kornman et al., 1997].

The same advantages of first-trimester screening were revealed by a Dutch survey of 99 pregnant women aged 36 and older. Of these women who participated in serum screening at 16 weeks' gestation, 82% would have preferred first-trimester screening [Weinans et al., 2000].

Mulvey and Wallace interviewed 100 women who had expressed willingness to participate in prenatal Down syndrome screening during their first prenatal visit, in order to determine their preferences and opinions regarding first- and second-trimester screening. The interview was based on a structured questionnaire with two sections, one for evaluating the women's knowledge of Down syndrome and the available screening and diagnostic techniques, the other for exploring their attitudes and preferences regarding first- and second-trimester screening. Assuming the same detection rate for first- and second-trimester screening, most of the women (74/100) preferred first-trimester nuchal translucency measurement to second-trimester markers. As reasons, they cited the earliness of the screening, the possibility of seeing the baby and detecting other abnormalities, the fear of blood tests, and the perception that ultrasonography is easier. The women who preferred second-trimester markers (26/100) cited instead the risks associated with ultrasound and the test's accuracy and ease of performance. Sixty-nine of the women would choose nuchal translucency measurement even if all affected fetuses diagnosed during the first trimester would abort spontaneously before the second trimester. Their reasons were the possibility of knowing the cause of the miscarriage and the desire to know whether or not the fetus had Down syndrome, regardless of the outcome of the pregnancy [Mulvey and Wallace, 2000].

10.2 Repercussions of false-positive results

One of the main drawbacks of prenatal screening, be it first-trimester or second-trimester, is the high number of false-positive results. Some of the consequences of false-positive results are the anxiety that they can cause in women, which can persist even after a negative prenatal diagnosis, the use of

diagnostic procedures that can cause an unaffected fetus to abort, and the impact of multiple testing on health-care costs.

Rausch et al. examined the repercussions of false-positive results on the participation of women in prenatal screening during subsequent pregnancies. The study involved an experimental group consisting of 108 women who were screen-false positive for Down syndrome or open neural tube defects during a previous pregnancy and a control group consisting of 108 women who were screen-negative, with the two groups matched for maternal age at the time of the second pregnancy. The authors concluded that the women in the screen false-positive group participated significantly less during their next pregnancy (57% vs. 79%, $\chi^2 = 11.27$; $p = 0.001$). The degree of risk does not seem to be a factor in the decision not to participate, but the authors postulate that the anxiety caused by a false-positive result has an influence on the level of participation [Rausch et al., 2000]. It is therefore important to improve screening techniques in order to reduce the false-positive rate as much as possible.

In addition, during first-trimester screening, one can use diagnostic techniques, such as amniocentesis or chorionic biopsy, earlier during the pregnancy. However, these techniques carry a greater risk than second-trimester amniocentesis, hence the importance of reducing the number of false-positive results.

10.3 Repercussions of false-negative results

Few studies have looked at the psychological consequences that a false-negative prenatal screening result can have on the parents of Down syndrome children. Hall et al. examined this matter in 179 families (179 mothers and 122 fathers) of Down syndrome children with the following breakdown: 86 mothers and 55 fathers had received a false-negative prenatal screening result; 59 mothers and 44 fathers had not been offered screening; and 34 mothers and 23 fathers had declined to participate. It was found that the parents who had received a false-negative result had more difficulty adjusting to having an affected child. The mothers experienced greater parenting stress ($p = 0.016$) and had more negative attitudes toward their child ($p = 0.009$) than those who had declined screening. Both the mothers and fathers blamed others, namely, health professionals or the health-care system in general, for the birth of an affected child after a false-negative screen. The comparison showed significant differences both for the group that had not been offered the test and the group that had declined it. Despite its limitations (sample not representative because of a high nonparticipation rate, the large number of exclusions due to discrepancies between the information obtained from the respondents and that in their medical files, and the exclusion of parents of children under the age of 2 years), the study shows that a false-negative result on prenatal screening can have an adverse effect on parental adjustment, measurable two to six years after the birth of an affected child [Hall et al., 2000].

In a recent systematic review, Petticrew et al. examined the impact of false-negative results in different screening programs and their implications. According to the authors, false-negative results occur in all screening programs, especially when the test is a qualitative one subject to interobserver variability. Furthermore, they note that few studies have examined the psychological effects of false-negative results. Studies also call attention to the legal (lawsuits arising from a missed or late diagnosis, especially in the United States) and economic (high cost of treating undetected diseases or more severe cases because of a late diagnosis) consequences. There seems to be a

consensus regarding the consequences of false-negative results on public confidence in screening programs, although these consequences have not been clearly demonstrated. In an attempt to resolve the problems posed by false-negative results, Petticrew et al. recommend that emphasis be placed on providing patients with information on both the benefits of screening and its limitations and consequences. Research should be conducted to determine the most effective means of informing participants, to assess the long-term psychological consequences of false-negative results, and to explore the public's perceptions and attitudes [Petticrew et al., 2000].

10.4 Attitudes toward prenatal screening and informed consent

Gekas et al. report the results of a survey conducted in France in 1997 among 504 women who had been advised to undergo amniocentesis following a second-trimester triple-marker screen-positive result. Serum screening has been in operation in France since 1989. The questionnaire, which consisted of 24 multiple-choice questions, explored the women's knowledge of the test's accuracy and interpretation, their knowledge of amniocentesis and their propensity to agree to a termination of pregnancy if the fetus had Down syndrome. Two hundred women answered the questionnaire. Prenatal maternal serum screening was recommended by a health professional in 42.5% of the cases, imposed as mandatory in 41.5% of the cases and performed without the woman's consent in 16% of the cases. The test results were communicated to the women by telephone (54.5%), by letter (19%) or during a follow-up visit (26.5%). Most of the women understood the purpose of the test, i.e., screening for Down syndrome, but 18.5% of them thought the test could provide information about all fetal malformations. Most of the women (67.5%) were not aware of the possibility of a false-negative result. In addition, 60% of the women were not aware of the possibility of undergoing amniocentesis before a test shows a high risk. The very day of the amniocentesis, 38.5% of the women were not aware of the risk of miscarriage associated with the procedure. Furthermore, 71% of the women considered the information they received about Down syndrome to be inadequate [Gekas et al., 1999]. Although these results cannot be generalized, they indicate that women who participate in prenatal screening and diagnosis are not well informed.

Another survey conducted in France among a general population of women who had participated in second-trimester serum marker screening yielded the following results: 90.5% of the 1,473 respondents indicated that there had been an interview before the test was ordered; 61.2% of the women were satisfied with the clarity and quantity of the explanations provided, 57.6% felt that the information helped them decide to undergo or decline screening; and 54.1% of them were satisfied with the explanations they were given of the test result. Amniocentesis was offered to 125 women; and 79.2% of them indicated they were willing to undergo the procedure. These women's opinions of the explanations of the test result were similar to those of the women who declined amniocentesis or who had not yet reached a decision about it. These findings point to the need to improve and individualize the information provided by health professionals, bearing in mind that decision making on the part of women requires the rapid integration of complex information. The survey shows that women are often dissatisfied with the information that accompanies the offer of testing and especially with the information provided when the result is communicated. Furthermore,

this information can be inadequate to help them make an informed decision and prepare them for the consequences of the screening, once they have made their decision. However, the authors were unable to establish a direct relationship between satisfaction with the information and decision assistance. Information can be considered a decision-making aid, even if the explanations are not understood. Decision assistance does not have the same meaning, depending on whether or not the test is presented as a routine procedure. Lastly, "best possible" decision-making by a woman requires the convergence of the health professionals' preferences regarding the information to be provided, of the woman's expectations in this regard, and of her preferences in terms of her involvement in the decision-making process. In conclusion, considering, from an operational standpoint, the use of information aids and decision-making aids could make explaining preferences and expectations easier [Seror et al., 2001].

A similar finding was made in another survey. It showed that more than 30% of the women surveyed did not realize, at the time the screening was performed, that the results could force them to make a decision concerning the loss of their fetus [Rüegsegger, 2001]. Implementing prenatal screening, which would guarantee the exercise of an informed choice by women, is a major challenge because of the time required for genetic counselling [Santalahti et al., 1998].

In 1999, Moyer et al. published the results of a study aimed at elucidating the factors that can influence women's decisions regarding prenatal screening and diagnosis, and at learning about their impressions and experiences. Eighty-one volunteers participated in the study, six of whom took part in the pilot phase. The study consisted in holding 2-hour group interviews and in administering a written questionnaire containing open- and closed-ended questions. It was found that most of the respondents considered prenatal screening tests (98%) and prenatal diagnostic tests (93%) useful or very useful. In addition, a vast majority of them also thought it was very important to have a child without a problem like Down syndrome (77%) and to avoid any risk of miscarriage (83%). Sixty-four percent of the women thought that having a Down syndrome child would be a difficult experience, but one they could deal with, while for 26% of the women, the birth of a Down syndrome child would have been the worst possible outcome of their pregnancy. Half of the women would have been willing to terminate the pregnancy–during the first trimester (55%) or second trimester (49%)–if the fetus had Down syndrome. The women brought out the positive aspects of testing, namely, being able to choose and decide and the reassuring counselling, but also the negative aspects, i.e., anxiety and the lack of options. Testing impedes the normal process of pregnancy, and the very fact that the tests are available creates an imperative to use them. Many women value being able to make their own choices, whereas others would prefer not having to make them. The option of prenatal diagnosis, which has its inherent risks, seems to be a very difficult one for many women. In addition, many of them indicated that they were not adequately informed about Down syndrome [Moyer et al., 1999].

Al-Jader et al. interviewed 35 women under the age of 35 who were 20 weeks pregnant one to two weeks after the end of prenatal screening tests. The questions were semistructured, and the interview was recorded. The purpose of the survey was threefold: to determine if the women had made informed decisions based on their understanding of the screening process, to explore their attitudes toward maternal serum screening and voluntary termination of

pregnancy in the event of Down syndrome, and to evaluate the ways in which prenatal screening services could be improved. Most of the women indicated that they had not made an informed choice, since the tests had been presented as being routine. The better-educated women and those who already had children seemed to be better informed than the others. On the other hand, the small group of women who had declined prenatal screening tests (5 out of 35) were better educated and had a higher social status. This was not a representative sample of all the pregnant women in the region. Consequently, the results cannot be generalized [Al-Jader et al., 2000].

Sixty women participated in a qualitative study in Ontario based on semistructured interviews using the focus group method. The purpose of the interviews was to explore women's opinions and experiences regarding serum screening. The results of this study highlight the importance that women attach to the quality of the information they receive before being able to make an informed decision. The decision is based mainly on personal values, social support and the information provided. The women indicated that this information should be provided as early as possible during the pregnancy and that their physician is the person who should provide it [Carroll et al., 2000].

In summary, the literature shows that, when given the option, most women prefer first-trimester screening because the period of uncertainty is shorter and because they can terminate the pregnancy earlier, before fetal movements can be perceived, and with a lower risk of complications. False-positive results are a source of anxiety for pregnant women and lead to the increased use of invasive diagnostic procedures, such as amniocentesis, which carry the risk of iatrogenic loss of non-Down syndrome fetuses. Multiple testing also has repercussions on health-care costs. A false-positive result can affect a women's decision to participate in screening during a subsequent pregnancy.

False-negative results can have psychological effects on the parents, and they can also experience more difficulty adapting to their parental role, even many years after the birth of an affected child. However, very few studies have examined this. As well, false-negative results seem to undermine public confidence in screening. Although many women agree to undergo prenatal Down syndrome screening, it seems that they lack the necessary information for making an informed decision regarding their willingness to participate in such screening when the time comes. They indicate that they find the information health professionals provide to them to be of considerable importance in being able to make an informed decision.

11

THE OPINION OF PROFESSIONALS AND THE POSITIONS OF THE VARIOUS ASSOCIATIONS

11.1 The perspective of health-care professionals

A Finnish study compared the opinions of obstetricians/gynecologists, pediatricians and family physicians (n = 750) regarding fetal screening. The study, which was conducted in 1996, was an anonymous, postal questionnaire survey. The response rate was 74%. Most of the physicians, regardless of their specialty, felt that serum screening for Down syndrome and ultrasound screening for structural abnormalities should be accessible to all pregnant women. Both types of screening were already in operation in Finland at the time of the survey. Between 1 and 5% of the physicians surveyed thought that neither should be available. A minority of the physicians thought that other screening tests for more rare congenital diseases that cause mental retardation in early childhood (fragile X syndrome, aspartylglucosaminuria, neuronal ceroid lipofuscinosis) should be available on a large scale. As for the benefits of prenatal Down syndrome screening, the argument put forth most often was that of preventing the birth of a handicapped child. Enabling parents to better prepare for the birth of an affected child and reducing the costs associated with managing handicapped individuals were considered important benefits. The opinions expressed by the different specialists were broadly the same. As for the disadvantages of prenatal Down syndrome screening, the respondents considered two issues to be important, namely, the anxiety that false-positive results cause in women and the pressure on them to abort at a point when the pregnancy is already advanced, which is emotionally difficult. Most of the respondents did not think that prenatal Down syndrome screening increases negative attitudes toward affected individuals, while for some of the other respondents, this is a major disadvantage [Hemminki et al., 2000].

11.2 The position of professional associations and clinical guidelines

In 1999, the American College of Obstetricians and Gynecologists (ACOG) stated in its position paper that, while promising, first-trimester prenatal screening for chromosome, cardiac or other abnormalities using nuchal translucency alone or in combination with serum markers, was still investigational. The technique for measuring nuchal translucency and the very definition of nuchal translucency need to be standardized, and until studies confirm the effectiveness of such screening, it is not recommended for routine clinical use [ACOG Committee Opinion No. 223, October 1999]. To date, the ACOG position remains unchanged.

The Society of Obstetricians and Gynaecologists of Canada (SOGC) has published a number of clinical guidelines for prenatal screening and diagnosis. In 1999, the SGOC's Genetics Committee published an opinion document in which it recommended that second-trimester maternal serum screening programs for Down syndrome and neural tube defects be set up across Canada. The Committee recommended a dating ultrasound to improve screening performance and recommended that mechanisms be instituted to ensure the ongoing education of health-care providers and consumers, and the evaluation and quality assurance of the programs [Genetics Committee of the SOGC, 1999].

In June 2001, the SOGC published Canadian guidelines for prenatal diagnosis. In these clinical guidelines, which are an update of those published in 1993, the SOGC considers that maternal age alone is not a very useful method of predicting fetal chromosome abnormalities and that the different combinations of serum and ultrasound markers can now improve the Down syndrome detection rate and

reduce the false-positive rate. According to the SOGC, and as had previously been recommended by the Canadian Task Force on the Periodic Health Examination [Dick et al., 1996], *"[s]creening for chromosomal anomalies based on biochemical markers should only be considered within a comprehensive screening and prenatal diagnosis program including interpretation, education, and follow-up counselling"*. As specifically regards ultrasound markers, the SOGC reports the results of the study by Snijders et al. [1998] concerning risk determination based on combined maternal age and nuchal translucency measurement (detection rate, 72%; false-positive rate, approximately 5%). In addition, the SOGC states that the *"[p]rediction of the risk for fetal trisomies based on soft signs should conform to accepted criteria for a screening program and should only be done where facilities exist for adequate follow-up."* Further studies should be conducted to determine how ultrasound signs *"can be combined with other information such as maternal age or maternal serum screening to provide risk estimates"* [Prenatal Diagnosis Committee of the CCMG and Genetics Committee of the SOGC, 2001].

In Québec, in 2001, a report was prepared by an ad hoc committee and approved by three medical associations in Québec (medical biochemists, medical geneticists and obstetricians/gynecologists). The report examines prenatal Down syndrome screening and recommends the rapid implementation of a second-trimester prenatal screening program and the assessment, in a university setting, of first-trimester screening. The report also looks at the implementation modalities for prenatal screening applicable to the Québec context [Désilets et al., 2001].

11.3 The perspective of Down syndrome associations

In a position paper on prenatal genetic testing published in May 1999, the Canadian Down Syndrome Society states that prenatal Down syndrome screening, the objective of which is to identify affected fetuses and terminate pregnancies, can adversely affect the quality of life of individuals with Down syndrome in our community. This could happen if this approach leads to a reduction in funding and support services for these individuals and if society in general adopts a negative attitude toward them. However, the Society does support screening if performed with a view to providing improved care by enabling parents and health professionals to better prepare for the birth of an affected child. Participation in screening should be voluntary and be based on quality genetic counselling, and parents should be given enough time to decide if they wish to proceed with the test. The Society also recommends giving parents the opportunity to speak to parents of Down syndrome children [CDSS, 1999].

12

THE ETHICAL ISSUES

Prenatal screening and diagnosis raise various ethical issues which pregnant women and couples, health professionals, society and the public authorities need to address, and these issues are the same for first-trimester and second-trimester screening. In this chapter, we resume our discussion of the ethical issues published in a previous report [CETS, 1999].

In the case of chromosome abnormalities, prenatal screening and diagnosis does not provide a therapeutic option, and the only preventive measure possible for parents is termination of pregnancy. Because these techniques are available, pregnant women and couples are faced with difficult decisions, which have to be made within very short order, right in the midst of the pregnancy, when anxiety and emotions are running high [Santalahti et al., 1998b].

Parents should be informed of the limitations of screening and of the complications associated with diagnosis. They should also understand that a screening result indicates a risk and that it cannot guarantee that the fetus has or does not have a given chromosome abnormality. In many cases, the screening will indicate a high risk, even though the fetus is not affected, and the pregnant women will be exposed to the complications associated with the diagnostic procedures. In addition, some parents will have a Down syndrome child even if the screening result indicated a low risk.

Once the diagnosis is confirmed, a decision must be made to continue or terminate the pregnancy. When, for different reasons, the individual is opposed to abortion, prenatal screening and diagnosis can be a way to anticipate the abnormality and enable the parents to be better prepared at the time of birth.

Genetic counsellors should inform the future parents of the benefits, limitations and consequences of screening and diagnosis in an **objective and nondirective** manner [Murray, 1994]. Genetic counselling should enable the pregnant woman or the couple to make a decision as to whether or not to proceed with screening, after having received all the relevant information concerning Down syndrome and the other aneuploidies, the risk of having an affected child, and the risks and limitations associated with the screening and diagnostic procedures. The counselling should cover the social aspects of the life of a person with Down syndrome [Milner, 1993].

Universal access to screening could result in it being ordered systematically and thus violate the principle of autonomy. Screening would thus lose its objective of offering couples an informed choice and become a eugenic practice. It could even have repercussions on those who decline to be tested [Royal Commission on New Reproductive Technologies, 1993; Annas, 1996]. However, the systematic offer of screening would permit equal access, as there are differences in awareness from one social class to another.

Even if a woman accepts the possibility of an abortion, other ethical issues accompany prenatal diagnosis, such as the debate over selection of the unborn. In the case of Down syndrome, a diagnosis of affected fetus does not provide any information about the severity of the case, i.e., the degree of mental retardation and the presence or absence of associated organic malformations. In addition, invasive diagnostic procedures also carry the risk of spontaneous loss of unaffected fetuses.

Choosing an age or a risk level above which a diagnosis is performed based on a balance between the risk of giving birth to a Down syndrome child and the risk of iatrogenic loss of an unaffected fetus implies the notion that these two trials are the same for all pregnant women [Moatti et al., 1992].

Furthermore, adopting such an age or risk level, both for screening and diagnosis, implies that a certain number of cases will not be detected or diagnosed.

The decision to make prenatal screening tests available is the responsibility of the public authorities, and it should be accompanied by the willingness to offer all the services considered necessary and to ensure their quality. Given the importance of genetic counselling, particular attention should be paid to health professional training and the resources allocated to this aspect of clinical practice.

Each case averted lightens the economic burden on the community, specifically with regard to health and special-education services that affected children require throughout their lives. However, identifying fetuses with a congenital disease and performing abortions can reinforce the prejudices toward handicapped individuals and taint the perception, by an affected individual, his or her family and society in general, of the burden that he or she presents. Prenatal screening should not result in the reallocation of resources or a reduction in services for managing affected individuals or in the support that their families require [Milner, 1993].

13

DISCUSSION OF THE BENEFITS AND LIMITATIONS OF FIRST-TRIMESTER SCREENING

A number of first-trimester prenatal screening techniques for chromosome abnormalities have been developed. Some of them are still in the experimental stage. The search for new prenatal screening techniques is aimed mainly at achieving the best detection rate (by also reducing the number of false negatives) and in reducing, as much as possible, the false-positive rate, for false-positive results lead to the increased use of diagnostic techniques, such as amniocentesis and chorionic biopsy, which are invasive procedures that can cause the iatrogenic loss of unaffected fetuses. Table 10 provides a summary of these techniques and their efficacy solely for Down syndrome screening.

First-trimester serum markers have been investigated in a large number of studies, including several retrospective trials with high-risk populations. The detection rate might be comparable to that achieved with second-trimester serum markers, but this still needs to be confirmed, since the methodology used in most studies does not take the spontaneous abortion of Down syndrome fetuses between the first trimester and term into account. To date, no large published controlled trial has compared first-trimester and second-trimester marker screening in terms of performance.

The influence of the different factors, such as maternal weight and smoking, parity, fetal sex, the presence of type 1 diabetes and the mother's ethnic origin, and the necessary adjustments to the calculation of the multiples of the median (MoM) for serum markers have not yet been adequately evaluated in the case of first-trimester screening. Serum marker screening is not indicated in twin pregnancies, and the markers cannot be used to detect open neural tube defects.

Ultrasonographic nuchal translucency measurement between the 10th and 14th week of pregnancy can reportedly detect 80% of Down syndrome fetuses, but the false-positive rate is high. As with serum markers, this performance could be lower if the prevalence of Down syndrome during the first trimester rather than at birth is taken into account. Although nuchal translucency measurement has been studied in more than 150,000 pregnant women, including more than 500 cases of Down syndrome,

Table 10
Summary of the first-trimester prenatal screening tests

Test	Week of pregnancy	Detection rate (%)	False positives (%)
Serum markers combined with maternal age	8-13	62	5
Nuchal translucency combined with maternal age	10-14	80	2.6-8.3
Combined test (serum markers + nuchal translucency + maternal age)	9-15	76-100	5-14
Integrated test (first + second trimester)	10-18	85	1
Urinary metabolites	11-22	79	5
Fetal cells in maternal blood	No data to date		

there are still many outstanding questions concerning its performance when used on a wide scale in the general population.

To improve the effectiveness of nuchal translucency measurement, certain conditions must be met. They are summarized in a paper by Nicolaides et al. They include: 1) appropriate practical training for sonographers and auditing their results; 2) the availability, among others, of good-quality equipment with calipers that are accurate to within a decimal point; 3) making the measurement between 11 weeks and 13^{+6} weeks with the fetus in the neutral position; 4) the option of using the transvaginal approach when the measurement cannot be obtained transabdominally [Nicolaides et al., 2000].

Combining first-trimester markers (serum markers + nuchal translucency + maternal age) would improve the detection rate considerably while at the same time keeping the false-positive rate constant. Currently, two large studies are being conducted in the United States and in Europe in order to determine, among others things, the efficacy of first-trimester combined screening compared to second-trimester maternal serum marker screening.

Its technical performance and limitations aside, first-trimester screening is preferred by pregnant women when they have a choice. The reasons they cite are a shorter period of uncertainty and an earlier risk assessment, which enables them to terminate the pregnancy earlier, if need be. It offers the possibility of a diagnosis by amniocentesis around the 14th week of pregnancy or of an earlier diagnosis by chorionic biopsy, if this procedure is available. However, it should be noted that, in Québec, a first-trimester screening program would, to a large extent, be based on amniocentesis during the investigation of high-risk cases. Since amniocentesis carries a greater risk when performed before the 14th week and since the cytogenetic analysis can be expected to take an average of 14 days, a pregnant woman will not receive the results of the analysis until the 16th week of pregnancy at the earliest. The interval between the screening and a definitive diagnosis will therefore be at least one month in most cases. The psychological impact of such a long wait has not been assessed.

Early screening also has some drawbacks. It permits the identification of a certain number of affected fetuses that will, in any event, abort spontaneously before term [Morris et al., 1999]. Couples are faced with painful decisions that they would not have to make if they were not offered early screening [van Lith, 1996]. This also has repercussions on the decisions to be made during subsequent pregnancies [Kornman et al., 1997].

The practice of first-trimester prenatal screening may lead to certain changes in the current practice of prenatal follow-up, specifically with regard to the date of the first prenatal visit and the date of the first-trimester ultrasound [van Lith, 1996]. Apart from the fact that pregnancy follow-up can start later in some women than the recommended date for first-trimester screening, the little time available for making a decision is a definite disadvantage of early screening. Many women should make the decision to participate in screening nearly at the same time as they receive confirmation of their pregnancy [Kornman et al., 1997]. Genetic counselling should be offered at three different times: before screening, in order to help the woman decide whether or not to participate, after screening, in order to help her understand the result indicating a low or high risk and decide whether or not to proceed to diagnosis, and lastly, after confirmation of the diagnosis by amniocentesis or chorionic biopsy. The importance of informed decisions and the ethical issues for women and couples, health professionals and society in

general were examined in detail in a previous report on second-trimester prenatal screening and diagnosis [CETS, 1999]. The analysis and conclusions apply to first-trimester screening as well.

Although the efficacy seems promising, based on the results of controlled studies, the data are not clear when it comes to the effectiveness of prenatal screening once it is offered to the population. A recently published retrospective study compared the effectiveness of the different prenatal screening policies in effect in eight different regions of the United Kingdom. In all, 53% of the Down syndrome cases were detected (between 31 and 62%, depending on the region), either by second-trimester serum marker screening or second-trimester ultrasound nuchal translucency measurement performed because of advanced maternal age or because of the woman's obstetrical history. In most of the regions, a combination of methods was used. The false-positive rate (women who had been advised to undergo diagnosis) varied from 2.8 to 7.7%. Although certain limitations of this study should be taken into account, such as the high proportion of women aged 35 and older, the high incidence of Down syndrome (1:476) and the low screening uptake rate, the results suggest that, in practice, adding new screening techniques does not have the anticipated effects on the detection rate [Wellesley et al., 2002]. In addition, an evaluation of prenatal screening services carried out in the United Kingdom revealed that, even more than 10 years after they were instituted, the services offered and the results achieved are not uniform from one region to another and even from one hospital to another [UK National Screening Committee, 2001].

To overcome one of the more important limitations of prenatal screening, namely, false-positive results and their impact on the use of diagnostic procedures and the inherent risk of iatrogenic fetal loss, some authors have proposed an integrated test, which combines first- and second-trimester screening. This method has been the subject of a demonstration project in Ontario. It reportedly leads to a considerable reduction in the false-positive rate and is very sensitive. The main drawback of this method is that one has to wait for the results, sometimes for several weeks. At some centres, to avoid this wait, the personnel perform tests sequentially, disclosing the risk as the testing proceeds. This method, in addition to shortening the wait, enables physicians to react to an interim result indicating a high risk. However, the efficacy of this method is apparently lower. Further studies are needed to confirm these findings and to determine the best way to offer the tests and to combine their results.

First-trimester screening can be used to detect other aneuploidies and other fetal abnormalities, mainly cardiac malformations, but cannot be used to identify open neural tube defects. One must therefore check for potential open neural tube defects by second-trimester ultrasound. Lastly, measuring the levels of urinary metabolites and recovering fetal cells or DNA from maternal blood are promising techniques, although they are still investigational.

The economic considerations relating to first-trimester prenatal screening and diagnosis are not examined in this report, although they were in a previous report on second-trimester prenatal screening and diagnosis [CETS, 1999]. A number of important questions concerning the effectiveness of the techniques and the organization of care in Québec are still unanswered, with the result that an economic analysis seems premature. However, it is plausible that the cost estimates for the different second-trimester prenatal screening procedures could apply to the first-trimester procedures. A recent, systematic review of the published economic evaluations of

ultrasonographic prenatal screening for fetal abnormalities found differences between the cost studies in different settings. Furthermore, the authors observed major differences in the efficacy of ultrasound between the studies, the best performance being achieved by sonographers who have received appropriate training and acquired technical expertise and when they have the best equipment available [Bricker et al., 2000; Roberts et al., 2002].

Before a decision is made to institute first-trimester prenatal screening, a demonstration project should be carried out to define the implementation mechanics (genetic counselling, professional training, organization of screening by serum and ultrasound markers, follow-up and quality assessment), to establish medians in the population, and to assess the effectiveness and costs, especially because effectiveness data are lacking and since the costs and implementation mechanics depend considerably on the local context.

When we sent this assessment report to press, Wald et al. were publishing the results of a large study of prenatal Down syndrome screening, the SURUSS trial (Serum, Urine and Ultrasound Screening Study). This study, the first to compare the predictive performance of the different combinations of first- and second-trimester prenatal screening tests, could provide additional material for this report (see next page).

Twenty-five maternity units offering second-trimester maternal serum screening took part in the prospective study of Wald et al.* Pregnant women who attended their first prenatal visit between the 8th and 14th week of pregnancy between September 1996 and April 2000 were invited to join the study. Forty-seven thousand and fifty-three pregnant women (singleton pregnancies) participated. An ultrasound examination was performed during the first visit in order to confirm that the fetus was alive, to determine the week of gestation and to take at least three nuchal translucency measurements. A serum sample and a urine sample were obtained during the first visit and during the second trimester. However, the prenatal diagnosis was based solely on the results of the second-trimester screening, whether by the double, triple or quadruple marker, depending on the protocol in effect at the maternity unit.

The results of this study demonstrate the efficacy of the integrated test (first-trimester PAPP-A and nuchal translucency, measured at 10 completed weeks of pregnancy; second-trimester AFP, uE3, β-hCG and inhibin-A, measured between 14 and 20 completed weeks of pregnancy). With a Down syndrome detection rate of 85% and 1.2% false positives, the integrated test would be the best choice in terms of efficacy, safety and costs. It is more expensive because it involves several markers, but the low false-positive rate reduces the number of amniocenteses required and the number of iatrogenic fetal losses, thus avoiding the costs associated with them. However, the authors point out that the integrated test's feasibility and acceptability need to be confirmed in other studies. Those studies are in progress. Without a nuchal translucency measurement, one would obtain the same detection rate by integrating the first- and second-trimester serum markers, but with 2.7% false positives. Also, the first-trimester combined test (PAPP-A, β-hCG and nuchal translucency) is recommended in women who want an answer earlier, and the second-trimester quadruple marker (AFP, uE3, β-hCG and inhibin-A) is the test of choice for women who attend their first prenatal visit after the 14th week of pregnancy. The authors state that, at a constant detection rate, the cost-effectiveness of these four prenatal screening methods is similar.

The efficacy of the combined test is comparable to that of the quadruple marker, that is, 6.1% and 6.2% false positives, respectively, for a 85% detection rate. These performances are possible when the combined test is performed at 10 completed weeks of pregnancy and when the quadruple marker is measured between 14 and 20 completed weeks. As for nuchal translucency measurement, it would be beneficial to convert the measurement obtained in millimetres to multiples of the median, using the medians calculated by each sonographer rather than those for the centre or population. Furthermore, the test's performance would improve if at least three measurements were obtained and if the risk calculation were based on their mean. Obtaining a satisfactory nuchal translucency measurement seems to depend, among other things, on the make or model of the ultrasound machine.

The authors do not recommend the use of the double or triple marker or that of an isolated nuchal translucency measurement because of the higher false-positive rates (13.1%, 9.3% and 20.0%, respectively, for a 85% detection rate). They also point out the drawbacks of the sequential use of first- and second-trimester markers, which would double the false-positive rate. Lastly, the article concludes that urinary markers contribute little to the efficacy of prenatal screening.

* Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). Health Technol Assess 2003;7(11).

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CONCLUSIONS AND RECOMMENDATIONS

The review of the published data on prenatal Down syndrome screening leads us to the following conclusions and recommendations:

Conclusions

- The efficacy (under experimental conditions) of the different first-trimester prenatal screening modalities for Down syndrome and other aneuploidies is satisfactory, but it still needs to be confirmed because of the methodological limitations of most of the studies. Despite the numerous studies involving more than 150,000 pregnancies, there are still some questions regarding effectiveness, especially that of nuchal translucency measurement in nonexperimental conditions.
- At this time, it is impossible to state whether first-trimester or second-trimester screening is superior in terms of efficacy.
- Different first-trimester prenatal screening modalities are already available in Québec, both in the public and private sector.
- First-trimester prenatal screening enables pregnant women to obtain an earlier diagnosis than second-trimester screening. Consequently, they prefer this approach.
- Implementing first-trimester screening will require changes to current prenatal care practice, mainly with regard to the week of pregnancy during which the pregnant woman's first medical visit takes place, the number of ultrasounds and when, during the pregnancy, ultrasound is performed. Some of these changes are already being instituted in Québec.
- Prenatal Down syndrome screening should be included with all other prenatal screening activities and take into consideration the other diseases that these techniques might or might not be able to detect.

Recommendations

- Based on the current state of knowledge, implementing **wide-scale** first-trimester screening in Québec cannot be recommended. However, it is essential that current practices be guided in order to ensure the quality of the services provided. First-trimester screening should be performed only at university hospitals which meet the requirements for providing quality service and which agree to be evaluated. The primary objective of the evaluation would be to determine the effectiveness of the different modalities in the Québec context. It should also make it possible to define the characteristics of the population and the service network and to determine the professionals' training needs regarding the techniques and genetic counselling, the availability of suitable equipment and the costs associated with screening in Québec. It would also serve to determine the main aspects of developing and implementing quality control mechanisms, should the practice be expanded.
- The conclusions of the 1999 CETS report, which examined second-trimester screening and diagnosis, still hold[3]. Implementing second-trimester screening will make it possible to offer serum marker screening to

3. Those conclusions still hold, even though the economic analysis of second-trimester screening was not updated, as this was not one of the objectives of this report, and though the quadruple marker should replace the triple marker.

all pregnant women who want it. It may also serve to set up genetic counselling services, which will be useful for all other types of prenatal screening and diagnosis, as well. Eventually, it may become a complementary approach to or be replaced by first-trimester screening. The results of research currently under way will be used to compare first-trimester screening and second-trimester screening and their usefulness when used alone or in combination.

Since the results of the SURUSS* trial (Serum, Urine and Ultrasound Screening Study) were being published right when we sent this assessment report to press, the report's conclusions and recommendations need to be discussed in light of those results.

As regards the conclusions, we have expanded upon the second one:

- Since the efficacy of first-trimester screening (combined test) and that of second-trimester screening (quadruple test) are comparable, it cannot, at this time, be stated that either modality is superior to the other.

In addition, the results of the SURUSS trial confirm the recommendations of this assessment report, mainly with regard to:

- The usefulness of instituting second-trimester prenatal screening in Québec; and
- The need to first limit the practice of first-trimester screening to specialized centres in order to determine its effectiveness, feasibility, costs and organizational aspects in the Québec context.

Furthermore, new knowledge is to be added to this assessment, specifically:

- It is important to examine the conditions for the practice of nuchal translucency measurement, especially the technical performance of ultrasound equipment (makes and models).
- When used alone, certain markers, mainly nuchal translucency measurement, do not seem to be very effective.
- From a practical standpoint, the integrated test is effective, and the integrated test exclusively with first- and second-trimester serum markers can yield a good performance.

However, as the authors point out, studies under way will need to confirm the feasibility and acceptability of the integrated test.

* Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). Health Technol Assess 2003;7(11).

APPENDICES

Appendix A
Determining test performance[4]

This section explains a few concepts that are essential to understanding this report. We present here the method for determining the internal validity or performance of a test, i.e., the test's ability to detect the disease.

		Individuals: Affected	Individuals: Not affected	**Total**
Test result	+	TP	FP	**TP + FP**
Total	–	FN	TN	**FN + TN**
		TP + FN	TN + FP	**TP + FP + TN + FN**

TP: True-positive result (the individual has the disease, and the test result is positive)

FP: False-positive result (the individual does not have the disease, but the test result is positive)

FN: False-negative result (the individual has the disease, but the test result is negative)

TN: True-negative result (the individual does not have the disease, and the test result is negative)

- ***Sensitivity***: $\frac{TP}{TP + FN} \times 100$

  The ***sensitivity*** of a test is the proportion of all the affected individuals that the test is able to detect in the population. In this report, sensitivity is referred to as the ***detection rate.***

- ***Specificity***: $\frac{TN}{TN + FP} \times 100$

  The ***specificity*** of a test is the proportion of unaffected individuals confirmed not to have the disease by a negative test result. Its complement, ***1 – specificity,*** is the ***proportion of false-positive results.*** In this report, the complement of specificity provides an estimate of the number of non-Down syndrome fetuses that will be considered as being at high risk and is referred to as the ***false-positive rate.*** In such cases, one should check for the presence of other pathologies or a dating error and advise the pregnant women of the option of undergoing a diagnostic test.

- ***Positive predictive value (PPV)***: $\frac{TP}{TP + FP} \times 100$

  The ***positive predictive value,*** or the ***predictive value of a positive result,*** of a test is the probability of having the disease when the test result is positive. In this report, this value is the proportion of pregnancies with Down syndrome fetuses for which the test results are positive.

- ***Negative predictive value (NPV)***: $\frac{TN}{TN + FN} \times 100$

  The ***negative predictive value,*** or the ***predictive value of a negative result,*** of a test is the probability of not having the disease when the test result is negative. In this report, this value is the proportion of pregnancies with non-Down syndrome fetuses for which the test results are negative.

4. The reference for this section is Jenicek et al., 1995.

Appendix B

Description of studies

Table B.1

Description of studies that examined the efficacy of first-trimester serum markers (β-hCG and PAPP-A) combined with maternal age

Study	Week of gestation	Method Population	Results	Comments
Brambati et al., 1994 UK	8-12	**Retrospective** design. 19 cases of aneuploidy (13 DS and 6 others). 89 matched controls (1:5) selected at random among pregnancies of the same gestational age in women who had undergone a chorionic biopsy with a normal karyotype.	**Estimated detection rate** (5% FP): 78.9% (CI: 64.9 – 92.8%) (maternal age + PAPP-A + β-hCG).	Modelling and Monte Carlo simulation with derived distributions of Down syndrome cases and unaffected controls. The likelihood ratios were obtained for the cases and controls and incorporated into the gestational age distribution in England and Wales (1986-1988). The risk at term was estimated for each maternal age. Spontaneous fetal losses were not taken into account. The analysis did not include any correction for maternal weight, parity, tobacco use or other variables.
Wald et al., 1996b UK	8-14	**Retrospective** design. Pregnant women who were advised to undergo a chorionic biopsy because of their age. 77 DS cases and 383 controls. Matching: 1:5. Matched for maternal age, duration of storage of samples and gestational age.	**Detection rate** (5% FP): 62% (maternal age + PAPP-A + β-hCG). PPV: 1:67 (risk cut-off level of 1:300) (based on the prevalence of Down syndrome by maternal age group in the absence of screening and TP).	All the measurements were made in duplicate, and the mean was used. The outcomes of the pregnancies were not known. The samples from all the cases and the controls were tested in the same lot. When calculating the detection rate, the authors did not take into account the spontaneous fetal losses between the first trimester and term.
Casals et al., 1996 Spain	10-13	**Retrospective** design. 1,138 pregnant women who were advised to undergo a chorionic biopsy because of their age. 19 cases of Down syndrome.	**Detection rate** (5% FP): 42% (PAPP-A + β-hCG) 82% (PAPP-A + AFP) 66% (PAPP-A); 9% (β-hCG).	The low values for β-hCG may have been due to the fact that several pregnancies diagnosed by chorionic biopsy were destined to abort spontaneously.

Table B.1 (cont'd)

Description of studies that examined the efficacy of first-trimester serum markers (β-hCG and PAPP-A) combined with maternal age

Study	Week of gestation	Method Population	Results	Comments
Krantz et al., 1996 USA	10-13	**Retrospective** design. 22 DS cases. 483 controls.	**Detection rate** (5% FP): 68.2% (PAPP-A + β-hCG). **Estimated detection rate** (5% FP): 63% (maternal age + PAPP-A + β-hCG).	To obtain an unbiased estimate, the detection and false-positive rates were calculated and modelled using the maternal age distribution for live births in the United States.
Forest et al., 1997 Canada	9-13	**Prospective** design. **Multicentre study** (6 centres). 10,160 women recruited between June 1989 and January 1995. The authors analyzed 18 DS cases and 500 pregnancies with unaffected fetuses. The following were excluded: diabetics, multiple pregnancies and fetuses with neural tube defects.	**Detection rate** (5% FP): 56% (95% CI: 33-79) (maternal age + PAPP-A + β-hCG).	The outcomes of the pregnancies were checked by examining the charts at each participating centre and by consulting the cytogenetic database. 25% of the pregnancies with Down syndrome fetuses ended in spontaneous abortion before the second trimester. These cases were excluded from the screening performance calculations. No correction for maternal weight.
Berry et al., 1997 UK	< 15	**Prospective** design. 10,600 serum samples collected over a 2-year period. Serum samples obtained for 54 DS cases during the first trimester. In 47 of these pregnancies, the first-trimester sample was paired with a second-trimester sample from the same pregnancy.	**Detection rate** (5% FP): 60% (maternal age + PAPP-A + β-hCG). **Estimated detection rate** (5% FP): 49% (95% CI: 34-62) (maternal age + PAPP-A + β-hCG). 55% (95% CI: 41-70) (β-hCG MoM:PAPP-A MoM ratio + maternal age).	The estimated detection rate was obtained by modelling using the pregnancy distribution by maternal age for Scotland. Comparison of first- and second-trimester screening: 60% vs. 87%, respectively.
Wheeler et al., 1998 Australia	9-12	**Retrospective** design. **Multicentre study** (8 centres). 713 women who were advised to undergo a chorionic biopsy. 17 DS cases and 18 other aneuploidies.	**Detection rate** (5% FP): 66.7% (maternal age + PAPP-A + β-hCG). **Estimated detection rate** (5% FP): 68.8% (maternal age + PAPP-A + β-hCG).	The authors used a computerized algorithm to combine maternal age and serum marker levels in order to determine screening efficacy. Karyotyping performed in all cases. Since most of the pregnancies with aneuploid fetuses were terminated voluntarily, how many of them would have ended in live births cannot be determined. Detection rate estimated for 10,000 women.

Table B.1 (cont'd)

Description of studies that examined the efficacy of first-trimester serum markers (β-hCG and PAPP-A) combined with maternal age

Study	Week of gestation	Method Population	Results	Comments
Haddow et al., 1998 USA	9-13	**Prospective** design. **Multicentre** study (16 centres). 3,217 at-risk women who were advised to undergo a chorionic biopsy. 48 DS cases and 3,169 unaffected pregnancies.	**Detection rate** (5% FP): 60% (95% CI: 45-74) (maternal age + PAPP-A + β-hCG).	Results not available for clinical follow-up. Karyotyping performed in all cases. 45% of the spontaneous losses of DS fetuses factored into the risk calculation.
Tsukerman et al., 1999 Belarus	9-13	**Retrospective design**. 11,659 serum samples tested for AFP and β-hCG; 13,477 were tested for AFP (11,659 plus 1,818). A subset of samples was tested for PAPP-A on a case-control basis where each case (n = 31) was matched with 50 controls (n = 1,564). Matched for gestational age and duration of storage of serum samples.	Predicted detection rate (5% FP): 69.1% (PAPP-A + β-hCG) 73.7% (PAPP-A + β-hCG + AFP).	None of the data from this study were used in the clinical management of the pregnancies. The MoM were adjusted for maternal weight. Statistical modelling that took the maternal age distribution of 104,000 women screened in Minsk between 1991 and 1997.

AFP: Alpha-fetoprotein; β-hCG: β-subunit of human chorionic gonadotropin; FP: False positives; CI: Confidence interval; MoM: Multiples of the median; PAPP-A: Pregnancy associated plasma protein-A; DS: Down syndrome; PPV: positive predictive value.

Table B.2
Description of studies that examined the efficacy of first-trimester ultrasound

Study	Week of gestation	Method Population	Risk cut-off level	Incidence of aneuploidies (per 1,000)	Incidence of DS (per 1,000)	Results	Comments
Savoldelli et al., 1993 Switzerland	9^{+3} to 12^{+5}	1,400 women who were advised to undergo a chorionic biopsy and karyotyping.	4 mm	31	20	**Detection rate** *DS*: 54% *Aneuploidies*: 44% FP: 0.4%	TA ultrasound. Of the FP (5 cases with increased NT and normal karyotype), 4 children were born normal and 1 fetus aborted spontaneously, 12 days after the biopsy.
Nicolaides et al., 1994 UK	10 to 13^{+6}	1,273 women with singleton pregnancies undergoing karyotyping because of their high risk.	3 mm	–	–	**Detection rate** *DS:* 84% *Trisomies*: 86% *Aneuploidies*: 72% FP: 4.5%	TA ultrasound. Two NT measurements were made in each case, and the higher one was used. Fetal karyotyping was performed in all cases.
Bewley et al., 1995 UK	8-13	1,127 pregnant women, 3 DS cases and 5 aneuploidies.	3 mm	4.4	2.7	**Detection rate** *DS*: 33% *Aneuploidies*: 40% FP: 6%	Outcome of pregnancy (second trimester and at term) determined from patient database and taken from information provided by the ultrasound unit, medical records, a cytogenetic registry, two surveys of the women and physicians, one postal and one by phone. Details of the pregnancy around the 20th week of gestation available for 98.5% of the women and, after birth, for 93%.
Brambati et al., 1995 Italy	8-15	1,819 pregnant women undergoing a chorionic biopsy and karyotyping because of a high risk.	3 mm	24	14	**Detection rate** *Aneuploidies*: 30% FP: 4%	TA ultrasound, with TV ultrasound in those cases were visualization was unsatisfactory. In all cases, NT was assessed by at least two sonographers. Two teams of sonographers at two centres (one public, one private).

Table B.2 (cont'd)

Description of studies that examined the efficacy of first-trimester ultrasound

Study	Week of gestation	Method Population	Risk cut-off level	Incidence of aneuploidies (per 1,000)	Incidence of DS (per 1,000)	Results	Comments
Comas et al., 1995 Spain	9-13	481 women with singleton pregnancies undergoing a chorionic biopsy.	3 mm	58	14.5	**Detection rate** *DS*: 57% *Trisomies*: 57% *Aneuploidies*: 50% FP: 9.9% or 0.7% (cut-off: 4 mm)	TV ultrasound. Outcome of pregnancy: karyotyping or perinatal follow-up confirming normal karyotype. Outcome known in 98% of the cases.
Hafner et al., 1995 Austria	10-13	1,972 women with singleton pregnancies. 4 DS cases.	2.5 mm	5.5	2	**Detection rate** *DS:* 50%; FP: 1.2% *Aneuploidies*: 73% FP: 0.9%	TA ultrasound. NT was measured in all cases (measurement successful in 100% of cases).
Pandya et al., 1995b UK	10-14	20,804 women with singleton pregnancies at four centres, and 76 specially trained sonographers. Maternal age was also taken into account.	> 1:100	7.9	4.1	**Detection rate** *DS:* 80% *Aneuploidies:* 79% FP: 4.9%	TA ultrasound, with TV ultrasound in those cases were visualization was unsatisfactory. NT was measured in all cases (measurement successful in 100% of cases). Outcome of pregnancy known in 20,557 cases. Lost to follow-up: 1.2% (247/20,804). Of these cases, 24 were karyotypically normal, and 223 had not been karyotyped.
Szabò et al., 1995 Hungary	9-12	1,280 with a high genetic risk. 2,100 low-risk women.	3 mm	28 4.3	20 1.9	**Detection rate** *DS*: 90% *Aneuploidies:* 94% FP: 1.6% PPV (aneuploidies): 44.8%	TV ultrasound. Outcome of pregnancy in the low-risk group known in 89% of the cases.

Table B.2 (cont'd)
Description of studies that examined the efficacy of first-trimester ultrasound

Study	Week of gestation	Method Population	Risk cut-off level	Incidence of aneuploidies (per 1,000)	Incidence of DS (per 1,000)	Results	Comments
Kornman et al., 1996 Netherlands	≤ 13	946 ultrasounds, 907 pregnant women and 923 fetuses. 16 multiple pregnancies were included in the study. 23 fetuses were examined twice. The second measurement was used. 475 high-risk women (52%). 432 (48%) at low risk.	3 mm	11	8	**Detection rate** *DS*: 29% *Aneuploidies*: 20% FP: 4%	TA ultrasound performed by four experienced sonographers properly trained in NT measurement. Outcome of pregnancy known in all but two cases. Measurement unsuccessful in 42% of the cases because of position of the fetus (15%), poor image definition (10%) and the size of the fetus (17%). Unsuccessful measurement was due to the short amount of time allotted to the examination (3 minutes) in an experimental setting.
Taipale et al., 1997 Finland	10-15.9	10,010 unselected women under the age of 40 with singleton pregnancies.	3 mm	2.6	1.3	**Detection rate** *DS*: 54% *Aneuploidies*: 69% FP: 1%	TV ultrasound. Slight manipulation of the uterus if the back of the fetus' neck could not be clearly visualized. Repeat examination after 30 minutes of walking, if necessary. Ultrasound performed by an obstetrician (11%) and by five specialized midwives. If the NT measurement was ≥ 3 mm, an examination was performed by at least two sonographers. If the NT was < 3 mm, an examination was performed by one sonographer. Outcome of pregnancy checked in all but 50 cases. Lost to follow-up: 0.5%. TV ultrasound did not reveal fetal abnormalities in any of the cases.
Thilaganathan et al., 1997 UK	10-14	3,604 pregnant women.	1:200	5	1.9	**Detection rate** *DS*: 71% *Aneuploidies*: 78% FP: 5%	Unsuccessful measurement: 9.4%.

Table B.2 (cont'd)

Description of studies that examined the efficacy of first-trimester ultrasound

Study	Week of gestation	Method Population	Risk cut-off level	Incidence of aneuploidies (per 1,000)	Incidence of DS (per 1,000)	Results	Comments
Hafner et al., 1998	10-13	4,233 women.	2.5 mm	1.6	0.94	**Detection rate** *DS*: 43% *Aneuploidies*: 65% FP: 1.7%	TA and TV ultrasound. Unsuccessful TA measurement: 2%. Ultrasounds performed by three experienced physicians. Several measurements taken in each case, with the mean used in the detection rate calculation. Outcome of the pregnancy known in all cases.
Pajkrt et al., 1998a Netherlands	10-14	2,247 women with singleton pregnancies to whom fetal karyotyping was recommended. 33 women were excluded because other fetal abnormalities were detected.	3 mm	28	16	**Detection rate** *DS*: 69% *Aneuploidies*: 48% FP: 4%	TA ultrasound. The measurement was considered unsuccessful in those cases where visualization of the back of the fetus' neck was impossible because of fetal position or maternal obesity (54/2,224, or 2.4%).
Pajkrt et al., 1998b Netherlands	10-14	1,473 women with singleton pregnancies. 6 fetuses (0.4%) excluded because of structural abnormalities detected on ultrasound.	3 mm	10	6	**Detection rate** *DS*: 67% *Aneuploidies*: 53% FP: 2.2%	TA ultrasound. Six experienced sonographers performed all of the examinations. They could take the necessary time to obtain a satisfactory NT measurement. In 64 of the 1,473 cases (4.3%), the measurement was unsuccessful because of fetal position. Outcomes of the pregnancies obtained through karyotyping and information provided by delivery room personnel. 68 cases (4.4%) lost to follow-up.
Snijders et al., 1998 UK	10-14	100,311 pregnant women; 306 sonographers at 22 centres. 4.2% (4,184) lost to follow-up. Sample: 96,127.	1:300 > 95th percentile	6.8	3.4	**Detection rate** *DS*: 82% *Aneuploidies*: 86% FP: 42.6%	Outcomes of the pregnancies assessed by karyotyping or examination of newborns. Calculation of the detection rate included maternal age (risk cut-off: 1:300) or according to nuchal translucency thickness (cut-off > 95th percentile).

Table B.2 (cont'd)

Description of studies that examined the efficacy of first-trimester ultrasound

Study	Week of gestation	Method Population	Risk cut-off level	Incidence of aneuploidies (per 1,000)	Incidence of DS (per 1,000)	Results	Comments
Theodoropoulos et al., 1998 Greece	10-14	3,550 consecutive pregnancies. Multicentre study (4 centres).	1:100 1:300	6	3	**Detection rate** *DS*: 82% *Aneuploidies:* 86% FP: 2.6% *DS*: 91% *Aneuploidies*: 95% FP: 4.9%	Sonographers with a certificate of competence from the FMF (London). TA ultrasound, with TV ultrasound in those cases where visualization was unsatisfactory. Outcome of the pregnancy known in all cases.
Schwärzler et al., 1999 UK	10-14	4,523 fetuses. Risk cut-off level adjusted on the basis of NT, maternal age, gestational age and obstetrical history.	1:270	5	2.6	**Detection rate** *DS:* 83% *Aneuploidies*: 78% FP: 4.7%	TA ultrasound (93%), with TV ultrasound (7%) in those cases where visualization was unsatisfactory. Outcome of the pregnancy obtained through questionnaires, karyotyping and examination of newborns by a neonatologist. Lost to follow-up: 26 (0.57%); excluded from study. None of them were at risk > 1:270. The fetuses with an NT > 2.5 mm were examined by two or more sonographers, but those with an NT < 2.5 mm by one sonographer only. In the cases of multiple measurements, the highest value was used. No limit on the amount of time for the ultrasound.
Thilaganathan et al., 1999 UK	10-14	11,398 unselected women. Ultrasounds performed by two midwives and five FMF-certified sonographers.	1:200	4.3	1.8	**Detection rate** *DS*: 76% *Aneuploidies*: 81% FP: 4.7%	TA ultrasound. Same amount of time available as for a routine ultrasound (5 min). Outcomes of the pregnancies obtained from medical records and physicians. Karyotype from cytogenetics laboratory. Unsuccessful measurements: 10%.

Table B.2 (cont'd)

Description of studies that examined the efficacy of first-trimester ultrasound

Study	Week of gestation	Method Population	Risk cut-off level	Incidence of aneuploidies (per 1,000)	Incidence of DS (per 1,000)	Results	Comments
Whitlow et al., 1999 UK	$11\text{-}14^{+6}$	6,634 women, 6,443 fetuses.	99th percentile	6.7	3.6	**Detection rate** *DS*: 65% *Aneuploidies:* 78% FP: 1%	TV ultrasound used in 20.1% of the cases. Outcome of the pregnancy known in 92.3% of the cases (5,947/6,443). Maternal age not factored into the detection rate calculation.
Zoppi et al., 2000 Italy	$10^{+3}\text{-}13^{+6}$	5,705 singleton pregnancies, 495 exclusions, 5,210 chosen for the analysis.	1:100 1:300	14	9	**Detection rate** *DS*: 70% *Aneuploidies*: 74% FP: 4.2% *DS*: 81% *Aneuploidies*: 89% FP: 11.1%	TA ultrasound, with TV ultrasound in those cases where visualization was unsatisfactory. Maternal age, gestational age and NT measurement factored into the risk calculation. High incidence of DS, despite the fact that this was an unselected population. 330 cases lost to follow-up (6.3%).
Acacio et al., 2001 Brazil	10-14	230 pregnant women examined at two private tertiary-care centres.	2.5 mm	100	52	**Detection rate** *DS*: 75% *Aneuploidies:* 70% FP: 12.5%	All the karyotypes were known. The detection rate was calculated in relation to the karyotype without taking into account the spontaneous fetal losses between diagnosis and term.
Brizot et al., 2001 Brazil	10-14	2,996 women with singleton pregnancies. Outcome of pregnancy not know in: • 3 cases with a risk ≥ 1:100 • 18 with a risk between 1:100 and 1:300 • 483 (17.4%) with a risk < 1:300. 2,774 cases included in the analysis.	1:100 1:300	7.3	3.3	**Detection rate** *DS:* 90% *Aneuploidies:* 82% FP: 3.1% *DS:* 90% *Aneuploidies:* 82% FP: 7.4%	TA ultrasound, with TV ultrasound in those cases where visualization was unsatisfactory. Risk calculation based on maternal age, gestational age and NT measurement. Ultrasounds performed by FMF-certified sonographers. Outcome of pregnancy known in 85.3% of the cases (2,557). Observed number of DS: 10 cases. Estimated incidence of DS: 11 cases. If the additional case was a false negative, the corrected detection rate would be 82% (9/11) instead of 90%.

Table B.2 (cont'd)
Description of studies that examined the efficacy of first-trimester ultrasound

Study	Week of gestation	Method Population	Risk cut-off level	Incidence of aneuploidies (per 1,000)	Incidence of DS (per 1,000)	Results	Comments
Gasiorek-Wiens et al., 2001 Germany, Switzerland, Austria	10-14	Multicentre study. 23,805 singleton pregnancies with live fetuses. 8% of the cases were excluded: 258 spontaneous abortions, 125 terminations of pregnancy, 1,463 lost to follow-up. 21,959 cases available for the analysis.	1:100 1:300	22	9.6	**Detection rate** *DS:* 80% *Aneuploidies:* 78% FP: 6% *DS:* 88% *Aneuploidies:* 87% FP: 13%	TA ultrasound, with TV ultrasound in those cases where visualization was unsatisfactory. TV in 3-5% of the cases. Ultrasounds performed by FMF-certified sonographers. Measurement successful in 100% of the cases.
Michailidis et al., 2001 UK	10-14	7,447 pregnant women.	99th percentile, or 95th for women > 37	–	3	**Detection rate** *DS:* 83% FP: 5%	TA ultrasound, with TV ultrasound in those cases where visualization was unsatisfactory. Retrospective calculation of the performance of NT measurement combined with maternal age.
Zoppi et al., 2001 Italy	10-14	12,495 women. 20% exclusions, including 1,422 cases lost to follow-up.	1:100 1:300	8.5	5.1	**Detection rate** *DS:* 77% *Aneuploidies:* 74% FP: 3% *DS:* 90% *Aneuploidies:* 88% FP: 9%	TA ultrasound, with TV ultrasound in those cases where visualization was unsatisfactory. TV in 0.2% of the cases. Ultrasounds performed by FMF-certified sonographers (5). Measurement successful in 100% of the cases.

NT: Nuchal translucency; FMF: Fetal Medicine Foundation, London; FP: False positives; DS: Down syndrome; TA: Transabdominal ultrasound; TV: Transvaginal ultrasound; PPV: Positive predictive value.

Table B.3

Description of studies that examined the efficacy of first-trimester combined test (serum markers[1], ultrasound and maternal age)

Study	Week of gestation	Method Population	Incidence of aneuploidies (per 1,000)	Incidence of DS (per 1,000)	Results	Comments
Noble et al., 1996 UK	10-14	**Prospective** design. 2,562 cases (including 61 DS fetuses). 41 DS cases included in a previous study.	–	20	**Observed detection rate** *DS:* 85% FP: 5%	Combined nuchal translucency with free β-hCG assay and maternal age. Information on the outcomes of the pregnancies obtained from maternity ward charts and patients. Exclusions: 50 cases of chromosome abnormalities other than DS, 10 cases of spontaneous abortion and 14 cases of termination of pregnancy following a diagnosis of fetal malformation.
Scott et al., 1996 UK	10-13	**Prospective** design. 302 cases, including 15 aneuploidies: 8 cases of DS, 4 cases of trisomy 18, and 3 triploidies. Risk cut-off: 1:250.	49	25.5	**Observed detection rate** *DS:* 87.5% FP: 14% **Estimated detection rate** *DS:* 71% (7% FP) *DS:* 58% (5% FP)	TA ultrasound. Combined nuchal translucency with free β-hCG assay and maternal age. Modelling of a population of 10,000 women. Pregnancy outcomes: No data.
Orlandi et al., 1997 USA	9-13^{+4}	**Prospective** design. 744 women (including 14 affected fetuses: 7 DS, 4 T18, 2 T13, 1 triploidy). Risk cut-off: 1:380.	19	9	**Observed detection rate** *DS:* 86% (95% CI: 42-100) FP: 4.7% (95% CI: 3.2-6.4) *DS + T18*: 91% (95% CI: 59-100) FP: 5.8% (95% CI: 4.2-7.7) **Estimated detection rate** *DS:* 87% (5% FP) T18: 76% (1% FP)	TA ultrasound. FMF-certified sonographers. Modelling using the observed rates and the maternal age distribution of live births in the United States. Verification of pregnancy outcomes: Not indicated.
Wald and Hackshaw,1997 UK	10-14	**Retrospective** design.	–	–	**Estimated detection rate** *DS:* 80% (5% FP)	Data from three studies were combined: Pandya et al., 1995b; Wald et al., 1996b; and Schuchter et al., 1997.

Table B.3 (cont'd)

Description of studies that examined the efficacy of first-trimester combined test (serum markers[1], ultrasound and maternal age)

Study	Week of gestation	Method Population	Incidence of aneuploidies (per 1,000)	Incidence of DS (per 1,000)	Results	Comments
Biagiotti et al., 1998 Italy	10-13	**Retrospective** design. 32 DS cases and 200 unaffected pregnancies.	–	9	**Estimated detection rate** 75.8% FP: 5%	TA ultrasound. Detection and FP rates estimated for an obstetrical population in Italy. If all affected fetuses destined to abort spontaneously (44%) could be identified during the first trimester, the anticipated detection rate at term would be 57%.
Benattar et al., 1999 France	12-14	**Prospective** design. 1,656 women. 7 aneuploidies: 5 DS, 1 T18 and 1 triploidy. Risk cut-off: 1:250. Serum markers: AFP and β-hCG.	4	3	**Estimated detection rate** 100% (95% CI: 48-100) FP: 9.7% (95% CI: 8.1-11.3)	TA ultrasound. Outcome of pregnancy not known in 18 cases (1.1%): 12 (0.7%) lost to follow-up, 2 abortions (one at 17 weeks, the other at 22 weeks), 2 cases of premature membrane rupture, and 2 stillbirths. No karyotyping in these cases.
De Biasio et al., 1999 Italy	10-13^{+6}	**Prospective** design. 1,467 women. Risk cut-off: 1:350.	–	9	**Observed detection rate** 85% (95% CI: 56-100) FP: 3.3%	TA ultrasound. Verification of pregnancy outcomes: Not indicated.
De Graaf et al., 1999 Netherlands	9-15	**Retrospective** design. 37 DS cases. 255 controls.	–	–	**Observed detection rate** 82% FP: 5%	TA ultrasound. Unsuccessful measurement: 4% (11/255 controls). Detection rate calculated for NT + PAPP-A + β-hCG (without maternal age).
Spencer et al., 1999 UK	10-14	**Retrospective** design. 210 DS cases. 946 controls.	–	–	**Estimated detection rate** 89%; FP: 5%. 70%; FP: 1%.	Detection rate estimated using the measured parameters PAPP-A and β-hCG, NT as per Snijders et al. [1998], and the maternal age distribution for England and Wales.

Table B.3 (cont'd)

Description of studies that examined the efficacy of first-trimester combined test (serum markers[1], ultrasound and maternal age)

Study	Week of gestation	Method Population	Incidence of aneuploidies (per 1,000)	Incidence of DS (per 1,000)	Results	Comments
Krantz et al., 2000 USA	10^{+4}-13^{+6}	**Prospective** design. 5,809 women Risk cut-off: 1:270.	16	5	**Estimated detection rate** • 91% (88% after an adjustment for spontaneous fetal losses); FP: 5%. • 70%; FP: 1.4%.	Ultrasounds performed according to the FMF protocol. Detection rate estimated for the entire U.S. population.
Spencer et al., 2000c UK	10^{+3}-13^{+6}	**Retrospective** design. 4,190 women.	5	2	**Detection rate** *DS*: 86% *T18/13*: 100% FP: 6.7%	Multidisciplinary one-stop clinic.

1. Serum markers: PAPP-A and β-hCG in all the studies, except those of Noble *et al.* [1996] and Scott *et al.* [1996] (β-hCG only), and the study of Benattar *et al.* [1999] (AFP and β-hCG).

NT: Nuchal translucency; FMF: Fetal Medicine Foundation; FP: False positives; DS: Down syndrome; TA: Transabdominal ultrasound.

Table B.4
Description of studies that evaluated women's experience of prenatal screening

Study	Objective	Method	Results and comments
Kornman et al., 1997 Netherlands	To examine women's opinions regarding the advantages of first-trimester vs. second-trimester screening.	Self-administered questionnaire. Group A: 181 women who came to a prenatal care clinic for a routine visit. Group B: 96 pregnant women referred to a prenatal diagnosis clinic because of their age or obstetrical history.	*Results:* Group A: 158 questionnaires analyzed. One hundred and nine women (69%) agreed to participate in second-trimester screening. Of these, 83 (76%) would have opted for first-trimester screening had it been available. The reason given most frequently was the possibility of terminating the pregnancy earlier, an easier course of action from both an emotional and technical standpoint. The second most common reason given was the shorter period of uncertainty. Group B: A third of the women would have agreed to first-trimester screening. *Comments:* Questionnaire available in the literature; no validation data.
Santalahti et al., 1998 Finland	To examine how women describe their decision-making during the different phases of prenatal screening and diagnosis.	Postal survey, but replaced with interviews because of the low response rate. Response rate: 79% (91/115).	*Results:* Most of the women said that participation in prenatal screening was presented to them as voluntary, but half of the respondents said they agreed to participate because they considered it routine. Only one-fourth of the women said they actively decided about participating in screening. The women's responses show the importance of the information provided. *Comments:* The questionnaire is not available.
Gekas et al., 1999 France	To assess participation, the level of satisfaction, and knowledge concerning serum screening and its consequences.	24-item, multiple-choice questionnaire mailed to women after a screen-positive result. Response rate: 39.7% (200/504).	*Results:* 42.5% of the women indicated that screening had been recommended by professionals, 41.5% indicated that it had been imposed on them, and 16% were screened without their consent. 58% of the women thought that screening was compulsory, being part of a pregnancy follow-up. *Comment:* The questions concerning the women's knowledge were selected on the basis of the genetic counselling and pregnancy termination unit's experience. The questionnaire was not validated, and the presurvey level of understanding was not assessed.

Table B.4 (cont'd)

Description of studies that evaluated women's experience of prenatal screening

Study	Objective	Method	Results and comments
Moyer et al., 1999 USA	To elucidate factors influencing women's decisions regarding prenatal screening and diagnosis.	Focus group and quantitative questionnaire administered after interviews to 75 participants.	*Results:* The wait is long and stressful; there is uncertainty due to false positives; the information on the risks posed by the procedures is not presented in an accurate manner; there is a lack of information on Down syndrome and living with an affected person; genetic counselling focuses more on the medical aspect than the social reality; etc. *Comments:* The questionnaire is not presented in the article.
Al-Jader et al., 2000 UK	To examine whether pregnant women made informed decisions based on an accurate understanding of screening and to explore their attitudes to screening.	Semistructured interviews with questionnaires. Population: 101 women under the age of 35 who were 20 weeks pregnant. Sample: 34 women.	*Results:* 9/23 women had sufficient time to make a decision regarding screening. Most of those who did not have enough time indicated that there was sufficient time, since they would have undergone screening in any case. Several of the women found that the information concerning risk provided by the professionals was too technical. Most of the women felt that the test was presented as a routine procedure, and few of them felt that they could have exercised a choice. *Comments:* The questionnaire is not presented in the article.
Carroll et al., 2000 Canada	To explore women's ideas, opinions, feelings and experiences concerning prenatal screening.	Qualitative technique of focus group. Six control groups consisting of women in various communities who had recently given birth.	Women aspire to make informed choices. They want information as early as possible, and they want it to be as complete as possible. They want to make decisions based on complete, personalized and unprejudiced information.
Hall et al., 2000 UK	To determine the psychological consequences for parents of children with Down syndrome of having received a FN result.	Retrospective study. Comparison of a group of parents who received a FN result with a group of parents who were not offered the test or who declined it. Semistructured interviews. Measurement scales used: STAI (Spielberger State-Trait Anxiety Inventory); Center for Epidemiologic Studies Depression Scale; Abidin Parenting Stress Index; Judson Scale (attitude towards disabled children); and a question about blaming others.	*Results:* Irrespective of participation in screening or of a false-negative result, parents adapt well after the birth of a Down syndrome child. The mothers who received a FN result experienced greater parenting stress and had more negative attitudes towards their child than those who declined the test. The parents who received a FN result were more likely to blame others. *Comments:* Scales known and validated.

Table B.4 (cont'd)
Description of studies that evaluated women's experience of prenatal screening

Study	Objective	Method	Results and comments
Mulvey et al., 2000 Australia	To determine women's preferences for first- or second-trimester screening.	Interviews with structured questionnaire. Two sections (12 questions on women's knowledge of Down syndrome and prenatal screening and diagnosis; 7 questions on preferences for first- rather than second-trimester screening.	*Results:* Most of the women had limited knowledge of Down syndrome and prenatal screening and diagnosis. If the detection rate were the same, most women (74/100) would prefer nuchal translucency measurement to second-trimester serum marker assays. 69/74 women still opt for first-trimester ultrasound, despite the possibility of the spontaneous abortion of all fetuses identified before the second trimester.
Rausch et al., 2000 USA	To determine whether women who have had a screen-positive result for Down syndrome or neural tube defect in one pregnancy have a lower screening uptake rate in their next pregnancy.	Information on the pregnancies and screening was obtained from the laboratory and databases. Two groups: 108 women who had a screen-positive result and 108 considered to be at low risk during a previous pregnancy.	*Results:* A result indicating a high risk during a previous pregnancy reduced participation in screening during a subsequent pregnancy by 64%. The degree of risk had no influence on participation in screening.
Weinans et al., 2000 Netherlands	To examine women's experience regarding prenatal Down syndrome screening.	Self-administered questionnaire. Group A (n = 99): women 36 years of age and older who were 20 to 36 weeks pregnant. Group B (n = 69): Women under the age of 36 who had a screen-positive result and who had subsequently undergone amniocentesis. Response rate: 82% and 91%, respectively.	*Results:* If serum screening had not been available, half of the women would have accepted amniocentesis. The others would have declined it. 82% of the respondents in Group A indicated that serum screening helped them make a better decision as to whether to undergo amniocentesis. Almost all of the women in this group said they would participate again in serum screening during a subsequent pregnancy. Most of the respondents (82%) would prefer first-trimester screening. Almost all the women in Group B (92%) experienced some degree of anxiety after they were informed of the screen-positive result. Slightly less than half of the respondents (41%) found the decision to undergo amniocentesis difficult, and 13% continued to experience anxiety, despite a normal karyotype. Fewer than 20% of the women indicated that they would not participate in screening during a subsequent pregnancy. *Comments:* The questionnaire does not appear in the article, and there is no information on its validation.

Table B.4 (cont'd)

Description of studies that evaluated women's experience of prenatal screening

Study	Objective	Method	Results and comments
Seror et al., 2001 France	To evaluate the practices of ordering and of communicating results and women's opinion of the information received and the decisions they plan to make.	Self-administered questionnaire (the women were given the questionnaire in the laboratory and returned it by mail). Response rate: 39% (1,490/3,825).	*Results:* 61% of the women were satisfied with the clarity and quantity of information provided, 58% felt that the information was useful in their decision-making, and 54% were satisfied with the explanations regarding the result. *Comments:* Questionnaire obtained from the authors. Validation done by another organization. Results not available.
De Vigan et al., 2002 France	To evaluate accessibility to screening and women's knowledge.	Questionnaire administered by interview immediately after delivery. Response rate: 92% (734/795).	*Results:* The women's knowledge of nuchal translucency screening was fragmentary and not as good as that of serum marker screening. Information on the interpretation and repercussions of an abnormal result was not provided or was not included in every case. The women who had an amniocentesis were not informed of the inherent risks in every case. *Comments:* Questionnaire not available; no information on its validation.

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Backgrounder

First-trimester prenatal screening for Down syndrome and other aneuploidies

Useful Links

Association de parents d'enfants trisomiques du Montréal Métropolitain

The mission of this organization is to bring together, support and inform parents of "trisomy 21" (Down syndrome) children, as well as anyone else interested in this syndrome; to inform and raise awareness among members of the public and school, medical and social authorities; and to promote the social and educational integration of trisomy 21 children. The association also encourages communication among its members with the goal of supporting these young people's physical and intellectual development.

633 est, rue Crémazie, 2e étage
Montréal (Québec), H2M 1L9
Telephone: (514) 850-0666
Fax: (514) 850-0660

E-mail: info@trisomie.qc.ca
Web site: www.cvm.qc.ca/jfmartin/trisomie/index.html

Association du Syndrome de Down de l'Estrie

The Association du Syndrome de Down de l'Estrie is a non-profit organization that supports parents of children with "trisomy 21 syndrome" (Down syndrome).

836, rue St-Charles
Sherbrooke, Qc J1H 4Z2
Telephone: (toll-free) 1 877 569-8112
Fax: (819) 569-5144

E-mail: asde_t21@hotmail.com
Web site: http://pages.infinit.net/trisomie/

Canadian Down Syndrome Society (CDSS)

The Canadian Down Syndrome Society (CDSS) is a national organization whose mission is to enhance the quality of life for all individuals who have Down syndrome through advocacy, education and providing information.

811 - 14 Street N.W.
Calgary, Alberta, Canada T2N 2A4
Téléphone: (sans frais) 1 800 883-5608
Télécopieur: (403) 270-8291

E-mail: dsinfo@cdss.ca
Web site: www.cdss.ca

Montreal Association for the Intellectually Handicapped

The mission of the Montreal Association for the Intellectually Handicapped is to employ all possible means to enable individuals with an intellectual handicap to take their places in society at every stage of their lives.

633, boul. Crémazie est, bureau 100
Montréal, Québec),H2M 1L9
Telephone: (514) 381-2307
Fax: (514) 381-0454

E-mail: amdi@delegation.ca
Web site: http://www.delegation.ca/amdi/

Useful Links (cont'd)

Association des obstétriciens et gynécologues du Québec (AOGQ)

This is an association representing all physicians holding specialists' certificates from the Collège des médecins du Québec in Obstetrics, Gynecology and Obstetrics/Gynecology. It was founded in 1966, following the consolidation of various groups of obstetricians and gynecologists in Québec.

2, Complexe Desjardins
Suite 3000, P.O. Box 216
Succursale Desjardins
Montréal, Québec, H5B 1G8
Telephone: (514) 849-4969
Fax: (514) 849-5011

E-mail: info@gynecoquebec.com
Web site: http://www.gynecoquebec.com/anglais/index.htm

Society of Obstetricians and Gynaecologists of Canada (SOGC)

The mission of the Society of Obstetricians and Gynecologists of Canada is to promote optimal women's health through leadership, collaboration, education, research and advocacy in the practice of this medical specialty.

780 Echo Drive
Ottawa, Ontario, K1S 5R7
Telephone: 1 800 561-2416
Fax: (613) 730-4314

E-mail: helpdesk@sogc.com
Web site: http://sogc.medical.org

International Federation of Gynecology and Obstetrics (FIGO)

The International Federation of Gynecology and Obstetrics is the only worldwide organisation that groups obstetricians and gynecologists. The mission of FIGO is to promote the well-being of women and to raise the standard of practice in obstetrics and gynecology.

70 Wimpole Street
London W1G 8AX
United Kingdom
Telephone: +44 20 7224 3270
Fax: +44 20 7935 0736

E-mail: figo@figo.org
Web site: http://www.figo.org

Biographical Notes

Renaldo N. Battista, M.D., M.P.H., Sc. D., FRCP (C)
President and Chief Executive Officer, AETMIS

Dr. Renaldo N. Battista is President and Chief Executive Officer of the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) and a full professor in the Epidemiology and Biostatics Department and the Medicine Department of the Faculty of Medicine at McGill University. An internationally recognized expert in his fields of expertise, Dr. Battista has been a member of the Scientific Advisory Board of the Agence nationale pour le développement de l'évaluation (ANDEM, Paris), the Board of Directors of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA, Ottawa), and the Scientific Advisory Board of the Catalan Agency for Health Technology Assessment (CAHTA, Barcelona). He also served for two years as Chairman of the Board of the International Society of Technology Assessment in Health Care (ISTAHC, Montréal). Since 2001, he has been a member of the Advisory Board of the Institute of Health Services and Policy Research with the Canadian Institutes of Health Research (CIHR).

Véronique Déry, M.D., M. Sc. (human nutrition)
Scientific Director, AETMIS

A physician specializing in public health, Dr. Véronique Déry has worked in hospitals in Laval and Pointe Claire, as well as in the private sector as Director of Scientific and Professional Affairs at Glaxo Canada from 1992 to 1994. Appointed consulting physician for the Direction de la santé publique de Montréal-Centre, she joined the team at the Institut national de santé publique in 1999, before being named Scientific Director of AETMIS in March 2002. Dr. Déry is also a consulting physician at the Centre pédiatrique de Laval and since 1988 has pursued an academic career at Université de Montréal, where she is an associate clinical professor in the Department of Social and Preventive Medicine. Dr. Déry received the *Coeur Québec Or* from the Québec Heart and Stroke Foundation in 2000 for her contribution to advancements in the prevention of cardiovascular disease, and in 2001 received the award for best professor from the Department of Social and Preventive Medicine in the Faculty of Medicine at Université de Montréal.

Alicia Framarin, M.D., M. Sc. (health administration)
Research Consultant, AETMIS

Dr. Alicia Framarin has served as a Consulting Researcher for AETMIS since 1996. She holds a medical degree from the University of Buenos Aires and a master's degree in Health Services Administration from Université de Montréal. She is an Associate Researcher at the clinical research centre of Centre hospitalier universitaire de Sherbrooke (CHUS) and spent four years as an advisor to the Association des hôpitaux du Québec OPTIMAH programs, whose purpose is to review medical practices. Dr. Framarin has been a consultant for Université de Montréal's international health unit since 2000, and since 1998, has worked with the Pan American Health Organization (PAHO) providing training courses to healthcare professionals and managers who carry out health technology assessment in Latin America.

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First-trimester prenatal screening for Down syndrome and other aneuploidies

AETMIS at-a-glance

The *Agence d'évaluation des technologies et des modes d'intervention en santé (*AETMIS*,* the Québec government agency responsible for health services and technology assessment) was created by the Québec Government on June 28, 2000, to replace the former Conseil d'évaluation des technologies de la santé (Council on health technology assessment). The mission of AETMIS is to assist and advise the Minister of Health and Social services, as well as decision-makers in Québec's health-care system, in matters concerning the assessment of health-care services and technologies.

AETMIS makes recommendations based on scientific reports assessing the introduction, distribution and application of health technologies, including technical aids for disabled persons and the delivery of health services. The assessments take into account multiple factors such as efficacy, security and efficiency, as well as social, ethical, organizational and economic implications. The range of topics covered is extremely broad, ranging from equipment and technologies to issues relating to health-care and services organization.

AETMIS is run by a Board chaired by AETMIS President and CEO Dr. Renaldo Battista. Some 15 expert members appointed by the Québec government Cabinet sit on the AETMIS Board. In addition, the agency has a steering committee representing Québec's main health-care organizations. Another of the agency's strengths is the diversity and complementarity of its approximately 30 researchers and professionals, whose expertise covers a wide array of disciplines, including health administration, bioethics, molecular biology, biotechnology, law, health economics, epidemiology, program evaluation, genetics, immunology, medicine, pediatrics, pharmacy and public health.

Not only does AETMIS produce and distribute assessment reports, it is also involved in promoting evaluation as a key decision-making tool. Thanks to a solid network of contacts at the national and international levels, AETMIS participates in several scientific forums and also supervises and trains graduate students. To find out more about AETMIS and works in progress or published reports, please visit its Web site or contact its management.

Mailing address:	2021 Union Avenue, #1040, Montréal, Québec H3A 2S9
Web site:	www.aetmis.gouv.qc.ca
E-mail:	aetmis@aetmis.gouv.qc.ca
Tel.:	(514) 873-2563
Fax:	(514) 873-1369