First-trimester prenatal screening for Down syndrome and other aneuploidies

SUMMARY

Agence d'évaluation des technologies et des modes d'intervention en santé

Québec

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Report prepared for AETMIS
by Alicia Framarin

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Agence d'évaluation
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et des modes
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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, distribution 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 implications.

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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 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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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 expensive and ineffective compared to what second-trimester maternal serum screening could offer. 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 10^{th} and 14^{th} 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 95^{th} 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, is 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 reproducibility 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 and colleagues. 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 performances, 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 11^{th} and 22^{nd} 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 should be able 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.

- Currently, 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 have 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 appropriate 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. 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.

Since the results of the SURUSS* study (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 study 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 efficacy, 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).

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

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.

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.

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).

False positives: All cases which are unaffected but which are considered at high risk upon screening.

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 a 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: Beta-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
TV: Transvaginal ultrasound
uE3: Unconjugated estriol
VTP: Voluntary termination of pregnancy