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ISSUES CONCERNING PRENATAL SCREENING AND DIAGNOSIS OF DOWN SYNDROME

Report submitted to

The Minister of Research, Science and Technology of Québec

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Conseil d'évaluation des technologies de la santé du Québec

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To promote and support health technology assessment, disseminate the results of the assessments and encourage their use in decision making by all stakeholders involved in the diffusion of these technologies.

To advise the Minister on matters concerning the introduction, diffusion and use of health technologies and, to this end, give advice based on the assessment of their effectiveness, safety and cost, their impact on the healthcare system and their economic, ethical and social implications.

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Note : This information about the mandate and the Conseil's members reflects the situation when the French official report was published. On June 28, 2000, the name and the mandate were modified and new members were appointed.

ISSUES CONCERNING PRENATAL SCREENING AND DIAGNOSIS OF DOWN SYNDROME

Down syndrome (DS) is a common chromosomal abnormality, and the risk of giving birth to an affected child increases with maternal age. In Quebec, pregnant women aged 35 and over have had access to prenatal diagnosis for some years, using amniocentesis followed by karyotyping during the second trimester of pregnancy. However, this costly and invasive technique presents risks for both mother and fetus, and is therefore unsuitable for use in all pregnant women.

DS prenatal screening using maternal serum markers is now available. This avoids amniocentesis-related problems, while permitting estimation of a pregnant woman's individual risk of having a child with DS. If the risk is considered high, amniocentesis is used to confirm the diagnosis.

The *Conseil d'évaluation des technologies de la santé (CETS)* was given the mandate by the *Ministère de la Santé et des Services sociaux* to assess whether it would be appropriate to introduce prenatal screening using maternal serum markers in Quebec. The assessment presented in this report is based on a cost-effectiveness analysis, accompanied by a description of DS, a review of the literature on the effectiveness of screening and diagnostic techniques, a study of existing programs and a discussion of ethical issues.

In conclusion, *CETS* considers that DS screening using serum markers should be made available to all pregnant women in Quebec, regardless of their age. Their participation should be voluntary, and they should freely give their informed consent after receiving complete, high-quality information from the professionals involved. The best screening strategy is one that enables more cases of DS to be diagnosed with the lowest risk of iatrogenic fetal loss at an acceptable cost, and that respects existing rights with respect to amniocentesis as of age 35. It must also be readily adaptable to new technological developments.

In disseminating its opinion, *CETS* wishes to provide the best possible information to decision makers concerned with this problem at various levels within Quebec's system of health and social services.

Renaldo N. Battista
President

SUMMARY

INTRODUCTION

Down syndrome (DS) is a common chromosomal abnormality, and the risk of having an affected child increases with maternal age. In Quebec, pregnant women aged 35 and over at the time of delivery have had access to prenatal diagnosis for some years, using amniocentesis followed by karyotyping during the second trimester of pregnancy. However, this costly and invasive technique presents risks for both mother and fetus, and is therefore unsuitable for use in all pregnant women. DS prenatal screening using maternal serum markers is now available and is free of such drawbacks. It also enables estimation of a pregnant woman's individual risk of having a child with DS. If the risk is considered high, amniocentesis is used to confirm the diagnosis. Several Canadian provinces and a number of countries in the world already make prenatal screening with serum markers available.

The *Conseil d'évaluation des technologies de la santé (CETS)* was given the mandate by the *Ministère de la Santé et des Services sociaux* to assess whether it would be appropriate to introduce prenatal screening using maternal serum markers in Quebec. This report presents a description of DS, a review of the literature on the effectiveness of screening and diagnostic techniques, a description of programs already available in Canada and elsewhere, and a cost-effectiveness analysis on introducing maternal serum marker screening in Quebec. Particular attention has also been paid to ethical issues inherent to DS prenatal screening.

DESCRIPTION OF DOWN SYNDROME

DS is the most common severe chromosomal abnormality known, and its incidence in the population is one in every 700 to 1,000 births. It can be caused by an extra chromosome at pair 21, a translocation or a mosaicism. Clinical presentation varies, but the phenotype is characteristic and is always accompanied by a certain degree of mental retardation. The risk of giving birth to a child with DS increases with the mother's age, and rises much more rapidly after age 35. Using the expected birth distribution for Quebec in the year 2000 and the risk based on maternal age, up to 111 cases of DS can be expected for that year.

DOWN SYNDROME PRENATAL SCREENING AND DIAGNOSIS

Prenatal screening covers the procedures available to all pregnant women in order to identify those at high risk of having a DS child. Risk is considered high when it exceeds a selected cutoff point, generally between 1:250 and 1:384. Screening can be carried out using serum markers or ultrasound, but new techniques are currently under development. The goal of prenatal diagnosis is to determine whether the fetus is, in fact, affected when screening has indicated a high-risk pregnancy. Amniocentesis and chorionic villus sampling are the diagnostic methods most commonly used.

Serum marker screening

Serum marker screening consists of measuring levels of specific markers in the maternal blood. The most often used markers are AFP, hCG and unconjugated estriol. Measurements are made during the second trimester, between the 15th and 18th week of gestation. The three markers are combined to form a "triple marker" test. However, other markers are also available, increasing the number of possible combinations. Serum markers are generally considered to provide a detection level of 65%, with a false positive rate of 8%. The detection rate represents the proportion of DS cases expected at birth that were detected by the test. The false positive rate represents the proportion of unaffected pregnancies for

which screening indicated an elevated risk of DS. While ultrasound is used in combination with the markers to confirm gestational age, it can also be used as a screening technique.

Some markers can be used during the first trimester of pregnancy. Although they render earlier diagnosis possible, their use is still not very widespread. New techniques are now being studied – the most promising are based on markers such as inhibin A or PAPP-A – but these must be validated before their use can be recommended.

Prenatal diagnosis

The prenatal diagnosis of DS is carried out by analyzing the karyotype of fetal cells obtained by amniocentesis or chorionic villus sampling. Amniocentesis can be performed during the first or second trimester, but presents greater risk for both mother and child in the former. It is therefore usually performed during the second trimester, and permits diagnosis of other chromosomal abnormalities. Sensitivity and specificity are near 100%. While the maternal risks associated with the procedure are small, it can cause iatrogenic fetal loss in 0.5 of cases, based on Quebec estimates.

The use of chorionic villus sampling is very limited in Quebec. This technique can be performed during the first trimester of pregnancy, but presents a greater risk of fetal loss and a higher rate of false positive and false negative results, in addition to being associated with an increase in fetal limb malformation. New diagnostic techniques are being developed, notably the identification of fetal cells in maternal blood.

The importance of genetic counselling

DS screening is based on the concept of risk, by permitting estimation of a pregnant woman's risk of giving birth to an affected child. Its major drawback, however, is that it generates a high number of false positive results. This means that women with an unaffected pregnancy but whose test results indicate they are at high risk are counselled to have amniocentesis, with the associated risk of iatrogenic fetal loss. It should be noted that DS screening and diagnosis take place during the second trimester of pregnancy and that, after screening, the mother and/or couple have limited time to make important decisions. If they agree to prenatal screening, they must receive all the necessary information so that they can understand the implications and make an informed choice. Genetic counselling is therefore indispensable if the nature and impact of the two risks involved are to be fully understood.

Current status of screening and diagnostic programs

In 1985, Manitoba became the first Canadian province to provide a provincial prenatal screening program using a single marker, AFP. Ontario followed in 1993 with a similar program that was based on the triple marker. In France, serum screening has been available at the national level for some years. Other European countries and the United States also offer such programs, although their modalities vary from country to country.

ETHICAL ISSUES

Prenatal screening and diagnosis raise a number of ethical questions for pregnant women and couples, health care professionals, society and government. DS screening and diagnosis offer no therapeutic solution, and the only preventive action possible is termination of the pregnancy. In view of this, voluntary participation of women and couples in DS screening is essential, and they must be able to count on objective, non-directing genetic counselling of high quality. Prenatal screening and diagnosis also raise other ethical issues, particularly with respect to the debate on selective birth. This debate is even more intense in the case of DS, since prenatal diagnosis pro-

vides no information on the degree of mental handicap nor the presence or absence of severe malformation. An additional consideration is the iatrogenic loss of unaffected fetuses. Finally, prenatal screening could lead to the reallocation of resources, which might result in fewer services being available to take care of affected individuals or provide support for their families.

SCREENING AND DIAGNOSTIC STRATEGY

This study analyzes various approaches to DS screening and diagnosis, which can be summarized as follows:

1) Amniocentesis, if 35 years and over at time of delivery (current situation in Quebec);
2) Universal maternal serum screening (MSS); amniocentesis if at high risk following serum test;
3) MSS if under 35, MSS or amniocentesis if 35 and over (current situation in Ontario);
4) MSS if under 35; amniocentesis if 35 and over;
5) MSS if under 37; MSS or amniocentesis if 37 and over;
6) MSS if under 37; amniocentesis if 37 and over.

The analysis in this report is performed from a public health perspective, the principal evaluation criterion being the cost-effectiveness ratio of the proposed approaches. The cost-effectiveness ratio is based on the cost per case diagnosed. We also considered the number of amniocenteses performed per case diagnosed and iatrogenic fetal loss per case diagnosed. Lastly, the analysis is based on the expected birth distribution for Quebec in 2000, actual and estimated costs of the various techniques in Quebec, effectiveness parameters reported in the literature, and current experience in Canada and elsewhere.

Cost-effectiveness analysis of the proposed approaches

The results suggest that the present program, which makes amniocentesis available to pregnant women aged 35 and over at time of delivery (strategy #1) is relatively expensive and ineffective. It would enable diagnosis of 28 cases of DS (out of 111 expected) at a total cost of $2.7 million and a C/E ratio of $97,965 per case. One hundred and ninety-seven amniocenteses would have to be performed for each case of DS diagnosed, and there would be 27 cases of iatrogenic fetal loss (ratio of iatrogenic fetal loss to cases diagnosed = 0.98). All of the other approaches considered appear to be more effective, with detection of 34 to 59 of the 111 cases of DS expected, a lower rate of iatrogenic fetal loss per case diagnosed and a lower C/E ratio (except in one instance, where the ratio is $112,544).

Strategy #2 (universal MSS; amniocentesis if at high risk) is attractive from the point of view of effectiveness with an acceptable C/E ratio, but would involve the loss of a current right – i.e. access to amniocentesis for women 35 years of age and over without prior screening. This right would be protected under strategy #3, with universal MSS and the choice of MSS or amniocentesis without prior screening for women 35 and over who want it. Almost 50% of DS cases would be diagnosed, with an iatrogenic fetal loss/case diagnosed ratio of 0.62, and a C/E ratio of $90,562 per case. The same approach, but with an age cutoff of 37 years (strategy #5), is more effective and has a lower C/E ratio ($79,664).

The best approach should be one that offers maternal serum screening to all pregnant women, maximizes the detection rate and minimizes iatrogenic fetal loss, allows women to make an informed choice and participate voluntarily, and preserves existing rights which, in Quebec, include the right to amniocentesis as of age 35.

CONCLUSION

The following conclusions were reached after this evaluation, which is supported by an in-depth review of the literature and a comparative analysis of various approaches to the screening and diagnosis of Down syndrome:

- *The Conseil considers that prenatal screening for Down syndrome using maternal serum markers should be made available to all pregnant women in Quebec, regardless of age.*

- *The participation of the pregnant woman in screening should be voluntary and based on informed choice, relying on complete, high quality information provided by first-line health care professionals (physicians, nurses, midwives, etc.) familiar with prenatal screening, and its benefits and limitations (false positive and false negative results).*

- *A woman's decision to undergo amniocentesis once prenatal screening indicates a high risk of Down syndrome or another chromosomal abnormality should also be voluntary and based on informed choice, relying on complete, high quality information provided by professionals trained in genetic counselling.*

- *The best screening strategy is one that permits more cases of Down syndrome to be diagnosed with the lowest risk of iatrogenic fetal loss at an acceptable cost. Selection of an age cutoff point for amniocentesis without prior screening should take existing rights into account, as well as the anxiety brought about by the possibility of having a child with Down syndrome for women aged 35 years and over.*

- *The screening and diagnostic strategy adopted for Down syndrome must be flexible, so that it can adjust rapidly to new technological developments*.

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LIST OF ABBREVIATIONS

AFP:	α-fetoprotein
CI:	confidence interval
CVS:	chorionic villus sampling
DNA:	deoxyribonucleic acid
DR:	detection rate
DRG:	diagnosis-related groups
DS:	Down syndrome
FISH:	fluorescence in situ hybridization
FPR:	false positive rate
FSH:	follicle-stimulating hormone
hCG:	human chorionic gonadotropin
	α-hCG: α subunit
	β-hCG: β subunit
IQ:	intelligence quotient
LH:	luteinizing hormone
MoM	multiple of the median
MSS:	maternal serum screening
PAPP-A:	pregnancy-associated plasma protein A
PCR:	polymerase chain reaction
PPV:	positive predictive value
TP:	termination of pregnancy
TSH:	thyroid-stimulating hormone
uE3:	unconjugated estriol

GLOSSARY

Abortion: Interruption of pregnancy before the 20th week of gestation, which corresponds to a fetal weight of approximately 500 g. Abortion can be early (before the 12th week) or late (between the 12th and 20th weeks). In this report, the terms abortion and fetal loss are sometimes used interchangeably.

Aneuploidy: An abnormal number of chromosomes being present, either due to the absence of a chromosome or the presence of an extra chromosome. The normal human karyotype contains 46 chromosomes, comprised of 22 pairs of autosomal chromosomes and one pair of sex chromosomes.

Balanced translocation: Alteration in the structure of two chromosomes, without any change in the quantity of genetic material. An individual presenting with a balanced translocation is a carrier but is unaffected by the chromosomal aberration.

Detection rate: The sensitivity of the test – i.e. its ability to identify affected subjects. It is closely related to the selected risk cutoff point and the false positive rate, but is independent of the prevalence of Down syndrome.

False negatives: Affected cases that remain undetected when screened.

False negative rate: The proportion of affected pregnancies considered to be at low risk on screening.

False positives: Unaffected cases considered at high risk when screened. The false positive rate is the complement of the specificity of the test (1-specificity).

False positive rate: The proportion of unaffected pregnancies considered to be high risk on screening. This rate is independent of the prevalence of Down syndrome and is equal to the complement of the specificity of the test (1 - specificity).

Fetal loss: Interruption of pregnancy after the 20th week and before the fetus is viable. In this report, the term "fetal loss" is used interchangeably with "abortion" in view of the difficulty in establishing the actual time point of the event in a particular pregnancy.

High risk after screening: The estimated risk is equal to or higher than the selected risk cutoff point. The risk cutoff ratio generally used when screening for Down syndrome is between 1:250 and 1:385.

Iatrogenic fetal loss: In this report, iatrogenic fetal loss refers exclusively to the loss of an unaffected fetus due to procedures intended for the diagnosis of Down syndrome.

Meiosis: Cell reproduction that results in the formation of the gametes (the spermatozoon and ovum). Unlike autosomal cells which contain 46 chromosomes (22 different pairs of autosomal chromosomes and one pair of sex chromosomes), gametes obtained through meiosis are haploid – i.e. they only contain 23 different chromosomes.

Mosaicism: The combination of more than one cell line, one of which presents a free trisomy or a translocation. This generally involves non-disjunction after formation of the zygote (i.e., the fertilized egg resulting from the combination of the two gametes, the spermatozoon and ovum).

Multiple of the median (MoM): Concentration of a serum marker in a pregnant woman divided by the median value of the marker concentration in all pregnant women at the same gestational age, after eliminating pregnancies with pathologies that might affect serum marker levels. An abnormal value is determined by one or more multiples of the median value, depending on the particular test.

Non-disjunction: An error in cell division that occurs during meiosis and which, in Down syndrome, results in the formation of gametes with two chromosome 21's. Trisomy 21 occurs upon fertilization by a normal gamete possessing one chromosome 21. Non-disjunction is not restricted to chromosome 21 and can give rise to other trisomies or a monosomy.

Phenotype: Manifestation of an individual's characteristics or make-up resulting from the interaction between his or her genetic background and environment.

Risk: In this study, risk is represented by the relationship between the number of affected and unaffected pregnancies, expressed as a ratio (e.g. a risk of 1:20 indicates 1 Down syndrome pregnancy for every 20 unaffected pregnancies) or as a proportion (e.g. a risk equal to 1/21, or 1 affected pregnancy out of 21 pregnancies).

Risk cutoff (point): An arbitrary value, which distinguishes high and low risk on screening.

Screening: The identification of a health problem in apparently healthy individuals. In the context of this report, screening refers to tests administered to pregnant women to detect whether they are at high risk of having a child with Down syndrome. Detection of an elevated risk does not confirm the diagnosis, but does suggest the need for diagnostic tests. (See table on next page for a comparison between Screening tests and diagnostic tests.)

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

Unbalanced translocation: Alteration in the structure of two chromosomes, involving a change in the quantity of genetic material present; an individual with this kind of translocation is affected by the chromosomal aberration.

References: [7, 103, 141]

Differences between screening and diagnostic tests [64]

Screening Test	Diagnostic Test
Intended to identify a health problem in an apparently healthy population.	Used to identify a health problem in an individual presenting specific problems.
A positive result does not confirm the diagnosis. It indicates an elevated risk of the disorder being present, and suggests the need for diagnostic tests.	A positive result confirms the diagnosis and is an indication to treat the patient.
Carried out on all individuals in a group.	Carried out on one individual.

EXPLANATORY NOTES

EVALUATION OF TEST PERFORMANCE[1]

This section introduces some of the concepts essential to an understanding of the report. It presents the method used to evaluate the internal validity or performance of a test – i.e. its ability to identify a given disease.

		Individuals		
		Ill	Healthy	Total
Test result	+	TP	FP	TP+FP
	-	FN	TN	FN+TN
Total		TP+FN	FP+TN	TP+FN+FP+TN

TP: True positive result (the individual is ill and the test is positive)
FP: False positive result (the individual is healthy but the test is positive)
FN: False negative result (the individual is ill but the test is negative)
TN: True negative result (the individual is healthy and the test is negative)

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

The **sensitivity** of a test represents the proportion of ill subjects that the test is capable of detecting in the population. In this report, sensitivity is called the ***"detection rate."***

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

  The ***specificity*** of a test represents the proportion of healthy subjects confirmed as such by the negative result of the text. Its complement (***1 - specificity)*** represents the ***proportion of false positive results***. In this report, the complement of the specificity permits estimation of the number of non-DS pregnancies considered at high risk (***false positive rate***). In such cases, the possibility of other pathologies or a dating error will be verified, and the pregnant woman will be counselled about the possibility of undergoing a diagnostic test.

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

  The ***positive predictive value*** of a test or the ***predictive value of a positive result*** indicates the probability of the individual being ill when the test is positive. In this report, it represents the proportion of actual DS pregnancies among those with positive results.

[1]The reference for this section is [64].

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

  The ***negative predictive value*** of a test or the ***predictive value of a negative result*** indicates the probability of an individual being healthy when the test is negative. In this report, it represents the proportion of non-DS pregnancies among those with negative results.

THE CONCEPT OF A RISK CUTOFF POINT

The selected risk cutoff point is closely related to the detection and false positive rates. Figure 1 shows the rates of detection and false positives for serum markers, based on a risk cutoff of 1:250. If the risk cutoff is shifted to the left (lower risk, e.g. 1:300, 1:385), the detection rate (sensitivity) improves, but with a concurrent rise in the false positive rate (1-specificity). If the risk cutoff is shifted to the right (higher risk, e.g. 1:200), fewer cases are detected by screening (lower detection rate), but there are also fewer false positive results.

Figure 1 represents the distribution of births and cases of DS expected in Quebec for year 2000, based on population projections [61] and the risk of DS at birth according to Cuckle et al. [34].

Figure 1: Detection and false positive rates using a risk cutoff point of 1:250