Prenatal Genetic Screening for Down Syndrome and Open Neural Tube Defects Using Maternal Serum Marker Screening

This Committee Opinion has been reviewed and approved by the Members of the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada.

This Committee Opinion has been prepared in consultation with the Members of the Ministry of Health of Ontario Committees.

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BACKGROUND

Prenatal screening for Down syndrome (DS) and open neural tube defects (oNTD) using markers in the maternal blood has become established in many centres. The screening method, known as maternal serum marker screening (MSS), is based on measurements of levels of alpha fetoprotein (AFP), unconjugated estriol (uE3) and human chorionic gonadotrophin (hCG) between 15 and 22 weeks of pregnancy. Assessments of various combinations of these markers, including total hCG and its alpha and beta sub-units, are in use in different jurisdictions. For simplicity’s sake, we will limit our discussion to triple marker screening (AFP+uE3+hCG). These measurements, used in conjunction with a woman’s age, provide an estimate of an individual’s risk of having a pregnancy with DS. By identifying the women at highest risk (about 8% of the screened population when the risk cut-off is 1/385 at term) and offering them amniocentesis, approximately 70 percent of DS fetuses can be detected. This detection rate (DR) is much higher than that achieved with prior methods of screening based on maternal age (present standard for invasive testing) or MSAFP alone. Maternal serum marker screening also results in a lower false-positive rate (FPR) and, thus, has the potential, following patient and physician education, to result in fewer amniocenteses while allowing screening to be available to all women (Table 1).

There have been several prospective intervention trials evaluating the efficacy of MSS in the detection of DS. All of these studies showed MSS to be more effective than age screening or MSAFP alone. In addition to screening for DS, the MSAFP component alone screens for oNTDs. The DR and FPR for oNTDs depends upon the MSAFP cut-off level chosen (e.g. 2.2 MOM), with most programmes achieving a DR greater than 80 percent at an FPR of less than five percent. The sensitivity approaches 100 percent when the AFP measurement is combined with a detailed ultrasound examination and the selective use of amniocentesis.

PRENATAL SCREENING FOR DOWN SYNDROME

SCREENING BASED ON MATERNAL AGE

Prenatal screening for DS has traditionally been limited to offering invasive testing to women 35 or older (the screening test is to ask a woman her age at the estimated date of delivery.) Women or their partners with a previous child with a chromosomal anomaly or those who are carriers of a chromosome rearrangement are also offered invasive testing. Maternal age is a poor screening test for Down syndrome because of its low DR and high FPR. The vast majority of DS infants would not be detected prenatally by age screening as they are born to women under 35 years of age.

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>PRENATAL SCREENING FOR DOWN SYNDROME</td>
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<table>
<thead>
<tr>
<th>Screening Method</th>
<th>False Positive (%)</th>
<th>Down Syndrome Detection Rate</th>
<th>Number of Down Syndromes Detected/ Amniocenteses Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk cut off =1/385</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal Age (MA) (≥ 35 years)</td>
<td>11.9</td>
<td>39.8</td>
<td>1/202</td>
</tr>
<tr>
<td>MA + MSAFP</td>
<td>12.2</td>
<td>49.8</td>
<td>1/166</td>
</tr>
<tr>
<td>MA + AFP, hCG, uE3</td>
<td>9.5</td>
<td>73.5</td>
<td>1/87</td>
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*MSAFP = Maternal serum alphafetoprotein
*hCG = Human chorionic gonadotrophin
*uE3 = Unconjugated estriol

SCREENING FOR DOWN SYNDROME USING MATERNAL SERUM SCREENING

With MSS, all pregnant women are offered screening in the second trimester and are provided with an estimate of the risk of their fetus being affected with DS. This risk estimate is derived from the individual tests of the three markers, which are combined with the maternal age-specific risk as well as maternal weight, race and insulin-dependent diabetes (IDDM) status to produce a summary probability that the fetus has DS. In women with a calculated probability exceeding a predetermined cut-off (1:385 risk of DS at the time of live birth, Province of Ontario), the gestational age is verified by ultra-
sound fetal biometry. If, on the basis of accurate fetal dating, the risks still exceed the cut-off, the woman is offered genetic counselling and amniocentesis.

As the concentrations of the three markers are highly dependent upon gestational age, and an error in gestational dating of greater than nine days can result in a large discrepancy in risk calculation, many experts recommend a routine dating ultrasound examination prior to screening. Studies have shown that the use of a dating ultrasound to establish gestational age prior to maternal serum screening decreases the FPR by as much as 50 percent, leading to a major reduction in the incidence of screen-positive women and, therefore, in the rate of amniocentesis and maternal anxiety.

Prenatal Screening for the Detection of Neural Tube Defects

Since the mid-1970s, it has been known that the level of AFP in the maternal serum is higher in pregnancies affected with oNTDs than in unaffected pregnancies. When screening for oNTDs, the AFP concentration is expressed in multiples of the median for unaffected pregnancies of the same gestational age. Screening is most effective between 16 and 18 weeks gestation when the distribution of MSAFP levels between affected and unaffected pregnancies is most widely separated.

The risks, benefits and limitations of AFP screening for oNTDs have been reviewed extensively, and it has come to be offered routinely in many centres throughout the world.

Prenatal Screening for the Detection of Trisomy 18

The maternal serum levels of AFP, hCG and uE3 are all depressed in the presence of trisomy 18. Using these markers, approximately 60 percent of cases of trisomy 18 can be detected with an FPR of 0.2 percent. It is, thus, possible to add trisomy 18 screening to the DS and oNTD screening protocol without altering greatly the overall FPR.

SOGC Committee Opinion

1. Should MSS be Introduced?

It is the opinion of the SOGC Genetics Committee that:

1) The maternal serum screen is a more effective and rational approach to aneuploidy screening for Down syndrome (trisomy 21) and trisomy 18 than screening based on maternal age or MSAFP alone.

2) Maternal serum AFP determination is an effective screen for fetal open neural tube defects with a high sensitivity and specificity when combined with a detailed ultrasound examination and selective use of amniocentesis.

3) Where feasible, screening for DS, trisomy 18 and oNTDs using MSS should be made available to all pregnant women in Canada.

2. How should MSS be Introduced?

Maternal serum screening is a non-invasive screening test. This means that most patients who are found to be screen positive for DS, T18 or oNTD will go on to have a normal baby, but such patients are eligible for genetic counselling and invasive diagnostic testing.

Proper interpretation of MSS results requires strict laboratory standards and accurate patient information. Inadequate patient and physician education and/or lack of facilities to interpret and follow up results can result in major problems.

For these reasons, the committee believes that if MSS is to be made available, it should be introduced as a provincially funded and centrally organized programme. At present, only Manitoba and Ontario have provincially funded serum marker screening. In Manitoba, provincially funded MSAFP screening was introduced in the 1980s, and efforts are currently underway to establish a multiple marker screening programme. In the Province of Ontario, provincially funded MSS was introduced in 1993. The Ministry of Health in Ontario felt that introducing centrally organized screening would allow for improved programme management, quality control of laboratory data and better patient care (Table 2).

Implementation of a Maternal Serum Marker Screening Programme

Implementation of MSS is considerably more complex than maternal age screening and requires many more resources: time for patient and physician education and patient counselling, as well as provision of addi-
The following factors must be considered in implementing MSS:

1. The programme should be funded centrally (e.g., provincial government). A multi-disciplinary implementation committee should be established to include representation from laboratory services, genetics, ultrasound, obstetrics, family practice, nursing, government and the public.

2. The provision of additional services may be required. These include: 1) ensured access and reasonable turn-around times (less than 5 working days), 2) obstetric and genetic services to provide genetic counselling, amniocentesis and cytogenetic services as well as detailed ultrasound.

3. Women should choose whether or not to have MSS in the context of informed choice. The information given to women prior to testing should include details about the conditions being screened, the likelihood of detection, the method of screening, the meaning of a screen-positive result and a screen-negative result, the choices following a screen-positive result (amniotic fluid alpha fetoprotein, acetylcholinesterase and fetal karyotype, detailed ultrasound for fetal anomaly), the choices following a positive diagnosis (abortion or continuation of the pregnancy) and details as to how further information can be obtained.

4. A method of providing appropriate educational information must be developed for both patient and health care provider (written information, video tapes, information brochures.) The decision whether or not to have testing may be verbally communicated between the woman and her health care provider but, ideally, should be recorded.

5. The risk cut-off for amniocentesis should attempt to achieve the optimal detection rate with the lowest false-positive rate. The detection rate varies according to the cut-off chosen. In Ontario, 1:385 was chosen because that is the DS risk in the 35-year-old woman at term. The uptake of amniocentesis given the screen-positive result for fetal aneuploidy has been approximately 86 percent. Figure 1 describes a sample protocol.

Policy for Women 35 years of age or over

Women who will be 35 at the estimated date of delivery should be offered MSS but should remain eligible for amniocentesis, regardless of the results. Many women in this age group do not wish initially to substitute screening for a definitive diagnostic test (e.g., chorionic villus sampling or amniocentesis). While this position may change as MSS becomes more established and both health care providers and consumers recognize the overall public health benefits of screening, it is essential that all couples understand...
that screening is not the same as diagnostic testing.

**CONCLUSIONS**

1. Introduction of a provincially funded and centrally organized MSS programme is recommended throughout Canada where local resources will permit and in the context described.

2. Dating ultrasound prior to screening markedly enhances the effectiveness of screening and should be recommended.

3. A mechanism to ensure the ongoing education of health care providers and consumers and the evaluation and quality assurance of the programme should be considered.

**REFERENCES**


