INTRODUCING A FIRST TRIMESTER PREGNANCY SCREENING TEST FOR FOETAL ABNORMALITIES

Introduction
Chromosomal abnormalities are important causes of prenatal death and childhood handicaps. A screening test indicating an increased risk for a chromosomal abnormality is the main indication for invasive prenatal diagnostic procedures.

The screening tests performed on maternal serum by measuring foeto-placental products, were traditionally determined in the second trimester of pregnancy. 90% of foetuses with open neural tube defects, 68% with Down syndrome and 65% with trisomy 18 were detected.

Incidence of foetal abnormalities

ONTD: (Open neural tube defect)
1 in 500 to 1000 live births
This occurrence is more common in some areas than in others
Should there be a history of a previously affected pregnancy the risk of an ONTD in the current pregnancy is increased by 5% (1 in 20)

Down syndrome:
1 in 666 (0.15%) live births
Advanced maternal age increases the risk:
• At 35 years of age: 1 in 385 (at birth)
• At 40 years of age: 1 in 105 (at birth)
40 - 50% of Down syndrome foetuses abort spontaneously

Trisomy 18:
1 in 8000 live births
Advanced maternal age increases the risk

Screening tests

1. The current second trimester screening test:
Valid between: 15 weeks and 20 weeks 6 days
Biochemical markers analysed on maternal serum - Triple test:
  - AFP (alpha - fetoprotein)
  - ß-HCG (total human chorionic gonadotrophin)
  - Estriol (unconjugated estriol)

Gestational age
The most accurate method to estimate the gestational age is by measuring foetal biparietal diameter by ultrasound.

Reasons: Estimation of gestational age according to dates may be inaccurate due to in-
regular menstrual cycles, uncertainty of last normal date of menstruation, differences in date of ovulation in spite of regular cycles.

Providing an accurate gestational age will increase the detection rate by 8 - 10% and decrease the cases of false positivity by 30% to 60%.

The gestational age should be expressed in weeks and days and not be rounded off.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>True positives</th>
<th>False positives</th>
<th>Affected foetuses in the case of positive screening test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONTD</td>
<td>90%</td>
<td>3%</td>
<td>1 in 10</td>
</tr>
<tr>
<td>Down</td>
<td>68%</td>
<td>5%</td>
<td>1 in 50</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>60%</td>
<td>1.2%</td>
<td>1 in 9</td>
</tr>
</tbody>
</table>

ONTD = Open neural tube defect

2. **Announcement of an alternative screening test**

**FIRST TRIMESTER SCREENING TEST**

Valid between:

- 10 weeks 3 days to 13 weeks 6 days
  - The measurement of the foetal nuchal translucency is the most accurate during this period.
  - Gestational age which is estimated by means of ultrasound, measuring foetal crown-rump length between 38 - 84 mm.

**Parameters** - a combination of foetal ultrasound measurement and biochemical analyses on maternal serum of foetoplacental products is required.

- **Biochemical analyses on maternal serum**
  - PAPP-A (Pregnancy associated plasma protein-A)
    - decreases in chromosomal abnormalities.
  - Free β-HCG (free beta human chorionic gonadotrophin)
    - increases in Down syndrome
    - decreases in trisomy 18 and 13

- **Ultrasound assessment**
  - Foetal nuchal translucency thickness (NT) (abnormal accumulation of fluid subcutaneously at the back of the foetal neck). It is recommended that the clinician should be accredited for these measurements to confirm accuracy.
    - increases with chromosomal abnormalities, inter alia Down syndrome, trisomy 18, trisomy 13, Turner and triploidy, as well as with non-chromosomal foetal abnormalities and in perinatal death.

**Maternal factors to be taken into account:**
Maternal age, weight, ethnicity, insulin dependant diabetes, para and gravida status, smoker.

Factors taken into account regarding recent pregnancy:

Multiple pregnancy and gestational age

Important remarks on first trimester screening

• Gestational age should be expressed in weeks and days and not be rounded off.
• A screening test in the first trimester should be at least 8.3% more sensitive than one in the second trimester, in order to compensate for spontaneous foetal losses after the first trimester.
• A chorionic villus biopsy is only safe after the gestational age of 10 weeks in order to prevent foetal limb reduction defects. The incidence of abortions related to this procedure is 1 - 2%.
• Other causes of a positive screening test:
  • Foetal death at gestational age of 18 - 22 weeks, foetal cardiac and/or renal complications, myotonic dystrophy, etc.

Advantages and disadvantages of the first trimester screening test

Advantages:
1. Should the patient's risk for chromosomal abnormalities be low, she can be put at ease early in her pregnancy.
2. In the event of a high risk, more time is available to decide on the diagnostic possibilities.
3. Should the patient decide on termination of an affected foetus, the procedure is safer and performed earlier in pregnancy.
5. Earlier diagnosis of multiple pregnancy.
6. It is less traumatic to terminate a pregnancy at an early gestational age, prior to the awareness of foetal movement.

Disadvantage:
Open neural tube defects can only be screened for, and detected in the second trimester of pregnancy:
Maternal AFP as screening test in the second trimester. High-resolution ultrasound and amniotic fluid AFP and -acetylcholine esterase as diagnostic tests.

3. A third choice of screening

A combination of first trimester screening test followed up by a triple test in the second trimester.
Should a detection rate of 80% be accepted for screening tests, the percentage of pregnant women who will have to undergo amniocentesis or chorionic villus biopsy, will differ as follows:

1st trimester combination test (NT + biochemistry) : 5%
2nd trimester triple test : 14.6%
Integrated 1st and 2nd trimester test : 1%

**Definitions**
- Detection rate (sensitivity): The portion of affected pregnancies with a positive result.
- False positive tempo (1 - specificity): The portion of normal pregnancies with a positive result.
- % of women who underwent a screening procedure and who needed an invasive diagnostic procedure:

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\text{Risk cut-off} = \frac{\text{True positives + false positives}}{\text{Total number of pregnancies screened}}
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**Diagnostic, invasive procedures**

The increased risk for a chromosomal abnormality, and in the second trimester also including ONTD, estimated with screening test, is a computer-based risk. An increased risk for Down syndrome is defined as a screening risk greater than 1 in 270 (equivalent to 1 in 385 at term). Based on age, this is equivalent to a maternal age of 35 years.

An increased risk should be confirmed by an invasive prenatal diagnostic procedure prior to the performance of any irreversible procedure (termination of pregnancy).
Confirmatory procedure in the first trimester:
Chorionic villus biopsy after the gestational age of 10 weeks or early amniocentesis.

Second trimester: amniocentesis

Confirmatory test for:
Chromosomal abnormalities: Genetic diagnostic tests namely, FISH and/or complete chromosomal studies on amniotic fluid.
ONTD (only in second trimester): AFP and acetylcholine esterase on amniotic fluid as well as a high-resolution ultrasound examination.

NB: A low risk (normal screening test) indicated by a screening test does NOT exclude a chromosomal abnormality conclusively and an increased risk does NOT necessarily indicate an abnormal pregnancy.

PROCEDURAL REQUIREMENTS FOR REQUESTING A FIRST TRIMESTER SCREENING TEST

1. 5ml clotted tube - the specimen is only suitable when centrifuged within 5 hours of collection.
2. Supply NT (foetal nuchal translucency), crown rump length as well as information requested on "First Trimester Down Screening Questionnaire".
3. Supply date of NT estimation. It is unnecessary for the NT and collection of blood sample to be performed on the same day. However, both should fall on or between 10 weeks 3 days and 13 weeks 6 days.
4. Two risks will be calculated: biochemistry only, biochemistry + NT.

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