ANTENATAL SCREENING FOR FETAL ABNORMALITIES IN HUNGARY

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ANTENATAL SCREENING FOR FETAL ABNORMALITIES IN HUNGARY

- Screening for Down syndrome
- Indications for prenatal invasive diagnosis
- Screening for structural anomalies by US
- Termination of pregnancy for fetal anomaly

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ISSUES

- PREVALENCE
- Screening strategies
- STRUCTURAL DEFECTS
- CHROMOSOMAL ABNORMALITIES
- MATERNAL AGE!!
- Too many choices!
- FUTURE TASKS
POPULATION FREQUENCY OF DISORDERS WITH GENETIC BACKGROUND

○ At birth: 4% (5-6%!)
○ At 1 year of age: 5 %
○ At 25 years of age: ~8%
  ○ monogenic
○ At 60 years of age: >90%
  ○ Polygenetic (complex)
## Annual Rate of Congenital Anomalies in the Earth (WHO)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
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<tbody>
<tr>
<td>Total no. of birth in the world</td>
<td>120,000,000</td>
</tr>
<tr>
<td>Congenit. struct. anomalies</td>
<td>2,890,000</td>
</tr>
<tr>
<td>Chromosomal anomalies</td>
<td>800,000</td>
</tr>
<tr>
<td>Mendelian disorders</td>
<td>700,000</td>
</tr>
<tr>
<td>Haemoglobinopathies</td>
<td>200,000</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>4,590,000</strong></td>
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CONGENITAL AND GENETIC DISORDERS

• Primary prevention
  folates NTD, CHD, rubella vaccination

• Preimplantation Genetic Diagnosis

• Secondary prevention
  Prenatal screening and
  Prenatal diagnostics
  Prenatal counselling

• Aim: Prenatal therapy!!!
Tertiary prenatal centers with cytogenetic labs in Hungary
ANTENATAL SCREENING FOR FETAL ABNORMALITIES IN HUNGARY

- Hungary was among the first countries applying **amniocentesis** in the late 70th and
- **chorionic villus** sampling in the early 1980th and prenatal diagnosis of fetal chromosomal abnormalities started.
- **weak govermental** support and the motor of the development was mainly
- **individual ambition/efforts** and enthusiasm characterizing outstanding activity of experts (ob/gyn, pediatr).
Screening for Structural Anomalies by Ultrasound
Screening for Congenital Heart Defects

- 1249 CHD out of 100 000 birth in 2005 (1.25%!)
- Prenatal detection rate: 2.49%
- Use of NT! approx: ~35-40%

Works only in experienced hands.
Screening for Neural Tube Defects

- Non-invasive screening for *fetal structural abnormalities* commenced in the early eighties by
  - ultrasound and
  - maternal serum alpha-fetoprotein (MS-AFP) determination.
Screening for Neural Tube Defects (2004)

- Anencephaly: 10/12 (83.3%)
- Spina bifida: 16/30 (53.3%)
- Encephalocele: 0/1
- Total No NTD: 26/43 (60.0%)
- Prenatal detection rate: 60 %
- Use of MS-AFP

Works only in experienced hands.
Prevalence of Neural Tube Defects in Hungary (1996-2006)

Anencephalia
Spina bifida
Encephalocele

HCAR(VRONY) (2008)
Rate of prenatally detected neural tube defects (1996-2006)

HCAR(VRONY) (2008)
Most efficient prenatal diagnostics
(Hungarian Congenital Abnormality Registry data, 2005)

- **Anencephaly**: 92.31%
  - 24 prenat.dg. out of 26 total
- **Other chromo abnorm.**: 77.78%
  - 35 prenat.dg. out of 45 total
- **Branchial arch abnorm.**: 68.75%
  - 22 prenat.dg. out of 32 total
- **Spina bifida**: 58.33%
  - 28 prenat.dg. out of 48 total
Less efficient prenatal diagnostics
(Hungarian Congenital Abnormality Registry data, 2005)

- Trisomy 21 65/152: 42.8%
- Polycystic kidney (7/35): 20%
- Urogenital obstr:30/317: 9.4%
- Limb reduction a.: 2/30: 6.7%
SCREENING OF CHROMOSOMAL ABNORMALITIES

Still present, and strong directive to invasive diagnostics from ob/gyn parties!

Irrespective of the level of risk obtained from screening.
SCREENING OF CHROMOSOMAL ABNORMALITIES

MATERNAL AGE!!!

ULTRASOUND markers:

- First-trimester
- Second trimester

MATERNAL BIOCHEMISTRY

- First-trimester: PAPP-a, freeß-hCG
- Second trimester: triple, quad-test

RISK ASSESSMENT based genetic counseling!!!
SCREENING OF CHROMOSOMAL ABNORMALITIES

MATERNAL AGE OF ≥35!!!

- Still present, and strong directive to invasive diagnostics from ob/gyn parties!
- Irrespective of the level of risk obtained from screening studies.
SCREENING OF FETAL CHROMOSOMAL ABNORMALITIES

FIRST-TRIMESTER: NT+NB
(FROM 1990, 2006)
The maximum thickness of NT should be measured!
Absent Nasal Bone in Trisomy 21 and 18

- **Normal**
  - 469
  - 3 (0.6%)

- **Trisomy 21**
  - 38
  - 29 (6.3%)
Aim of Prenatal Screening and Diagnosis Comes True with Ultrasound:

Holistic approach TO STOP
- not only RECURRENTCE, but
- firsts OCCURRENTCE!
EFFECT OF NT-SCREENING ON PRENATALLY DETECTED RATE OF TRISOMY 21 (1984-1999)
Rate of Prenatally Diagnosed trisomy 21 cases between 1984-2007 in South Hungary (US screening)

- Postnatal: n=486
- Prenatal: n=128
Policy offer of Hungarian Society of Ultrasound in Obstetrics and Gynecology for screening of fetal abnormalities

- **1st US:** 12 weeks
- **2nd US:** 18-20 weeks
- **3rd US:** 28 weeks
- **Works only in experienced hands. A, B, C level ultrasound examination**
Ultrasound screening for trisomies

Ultrasound markers in 1st trimester
- nuchal translucency √.
- nasal bone √?
- Frontomaxillary facial angle -
- Ductus venosus flow -
- Tricuspid regurgitation -

Ultrasound markers in 2nd trimester
- Nuchal pad √ -
- Heart defects √ -
- Nasal bone length √ -
- Dilatation of the lateral ventricle -
- Gastrointestinal tract √
- Urogenital tract. et cet. √
First-trimester maternal serum markers (at 10-12 week)

1. Free $\beta$-HCG↑

2. PAPP-A↓ (Pregnancy associated plasma protein-A)
Second-trimester screening for fetal aneuploidies

Biochemistry (16th week)
1. Free $\beta$-HCG and
2. AFP (alfa-fetoprotein)
3. Estriol
4. Inhibin-A

Quad test
MS SERUM ALPHA-FETOPROTEIN (at 16th week)

Elevated MS-AFP level:
1. NTD
2. VENTRAL WALL DEFECTS
3. MULTIPLES
4. I.U. DEATH, MISSED ABORTION
5. NEPHROSIS syndrome
6. Other

LOW MS-AFP level:
1. MISSED ABORTION
2. ANEUPLOIDIES
Screening approaches, TOO MANY CHOICES!

- Maternal age
- Combined in 1st trimester
- Contingency
- Combined in 2nd trimester
- Fully integrated test
- Sequential
Screening for fetal abnormalities

- There is a basic and fundamental principle of screening:
  - a screening test may be followed by a diagnostic test,
  - not another screening test!
Screening should not confuse us!

Avoid!

1. **Confusion**: patient, obstetrician, counsellor

2. Lack of **confidence** leading anger on the part of the patient.

3. “Which screening test do I believe?”
INVASIVE TESTS

Carry 1% risk of abortion!

Amniocentesis

CVS

Cordocentesis
Capacity of cytogenetic labs (increased false positive rate!).
DISTINGUISH between screening and diagnosis of Down’s syndrome!

- **CVS, amnio-, or cordocentesis**
- **1% fetal loss indicates that it can be recommended only to pregnant population with high genetic risk.**
- **Consequently:** the development of screening methods with high detection rate and with low false positive and negative rate is mandatory → **FOR EACH PATIENTS**
DISTINGUISH between screening and diagnosis of Down’s syndrome.

**Diagnosis:** Yes or no answer at present by cytogenetic-processing fetal cells obtained by CVS, amnio-, or cordocentesis.

~1% fetal loss
FETAL SAFETY!
Screening: NO HARM to the outcome of pregnancy

Fals positive rate: the % a pregnant population above the cut off

More sampling we perform, the more procedure related fetal loss will occur, in other words:

- Increasing the no. of sampling increase the
- iatrogenic pregnancy loss rate
- FETAL SAFETY!
Focus on safety!!

- We think along with others that prenatal screening for Down syndrome should focus not only on cost-effectiveness but on detection rate and fetal safety, which depends on reliability of a particular screening approach.
There are many tasks ahead us

- 1. selection and introduction of the most sensitive novel techniques,
- 2. continuous theoretical and
- 3. practical training and education,
- 4. refreshing guidelines by the clinical genetic board,
- 5. quality control.
- 6. Primary prevention
 VII\textsuperscript{th} DOWN SYNDROME SYMPOSIUM
MAY 16-17, SZEGED, 2008.MAY

- **DOWN SYNDROME: COMPLEX!!!**
  - Not only an issue "to screen it out"
  - Parental party
- **Ethics**
  INFORMED AND INTERPRET!
  * Mutual understanding !!
MAY I TEACH YOU?