Clinical Genetics
Congenital chromosomal aberrations

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Chromosomal aberrations

0.6-0.7% live born
Karyotyp 46,XY – normal in men
G-pruhy
Chromosomal aberrations

• **Inborn:**
  • 20 – 50% all conceptions
  • 50 – 60% abortions (I. trimester)
  • 0, 56 - 0,7 % live born

• **Acquired:**
  • Oncology – hematooncology
  • Risks in environment (drugs, cigarettes, …)
Congenital chromosomal aberrations

- Autosomes
- Gonosomes
- Numerous
- Structural
- Balanced
- Unbalanced
### Frequency of congenital chromosomal aberrations

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live-born children</td>
<td>0.6%</td>
</tr>
<tr>
<td>Balanced</td>
<td>0.2%</td>
</tr>
<tr>
<td>Unbalanced</td>
<td>0.4%</td>
</tr>
<tr>
<td>SA</td>
<td>50%</td>
</tr>
<tr>
<td>Still born children</td>
<td>11.1%</td>
</tr>
<tr>
<td>Newborns with congenital malformations</td>
<td>15%</td>
</tr>
<tr>
<td>Premature babies</td>
<td>2.5%</td>
</tr>
</tbody>
</table>
Chromosomal aberrations in spont. abortions

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>All spont. abortions</td>
<td>50 %</td>
</tr>
<tr>
<td>Up to 12 weeks</td>
<td>60 %</td>
</tr>
<tr>
<td>12-20 weeks</td>
<td>20 %</td>
</tr>
<tr>
<td>stillbirths</td>
<td>5 %</td>
</tr>
<tr>
<td>trisomies</td>
<td>52 %</td>
</tr>
<tr>
<td>45,X</td>
<td>18 %</td>
</tr>
<tr>
<td>Translocations</td>
<td>2 – 4%</td>
</tr>
<tr>
<td>Condition</td>
<td>Frequency</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>1,5 per 1000 live births</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>0,12</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>0,07</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>1,5</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>0,4</td>
</tr>
<tr>
<td>XYY syndrome</td>
<td>1,5</td>
</tr>
<tr>
<td>XXX syndrome</td>
<td>0,65</td>
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</table>
Cytogenetic analysis

- Prenatal

- Postnatal
Material for cytogenetic analysis

- Cells from amnionic fluid
- Chorion villi
- Placenta
- Fetal blood
- Tissue – aborted fetuses
- Peripheral blood lymphocytes
- Tissue (skin biopsy, bucal smear, …)
Indications for postnatal cytogenetic analysis

- The typical phenotype
- Newborn with multiple malformations
- Psychomotor / mental retardation
- Stigmatization
- Genital anomalies
- Disorders of sex development
- Infertile couples
- Gametes donors
Indications for amniocentesis

- Positive biochemical screening
- Pathological ultrasound findings in the fetus
- Balanced chromosomal aberrations in parents
- Chromosomal aberrations in the family
- Age of parents - ???
- Monogenic disease present in the family
<table>
<thead>
<tr>
<th>years</th>
<th>+21</th>
<th>+18</th>
<th>+13</th>
<th>XXY</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>3,9</td>
<td>0,5</td>
<td>0,2</td>
<td>0,5</td>
<td>8,7</td>
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<tr>
<td>37</td>
<td>6,4</td>
<td>1,0</td>
<td>0,4</td>
<td>0,8</td>
<td>12,2</td>
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<tr>
<td>40</td>
<td>13,3</td>
<td>2,8</td>
<td>1,1</td>
<td>1,8</td>
<td>23,0</td>
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<tr>
<td>43</td>
<td>27,4</td>
<td>7,6</td>
<td></td>
<td>4,1</td>
<td>45,0</td>
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<tr>
<td>45</td>
<td>44,2</td>
<td></td>
<td></td>
<td>7,0</td>
<td>62,0</td>
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<tr>
<td>47</td>
<td>70,4</td>
<td></td>
<td></td>
<td>11,9</td>
<td>96,0</td>
</tr>
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Down syndrome
Down syndrome

- 47,XX,+21 or 47,XY,+21

- About 1/800-1000 newborns, 1/75 SA
- Hypotonia, joint laxicity, soft skin, flat face, prominent intercanthal folds, slanted palpebral fissurs, Brushfield spots of the irides, small, down set ears, small nose, protruding tongue, simian crease in the hands (about 45%), short stature, mental retardation, congenital heart disease in about 50% of patients with DS, (atrioventricular canal)
Down syndrome (G-banding)

47,XY,+21
Happy nature

Vision and hearing disorders

Hypothyroidism

Correlation between positive stimulation and height IQ

Male sterility

Alzheimer-like symptoms in 40
<table>
<thead>
<tr>
<th>Maternal age (years)</th>
<th>Risk</th>
</tr>
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<tbody>
<tr>
<td>15</td>
<td>1/1578</td>
</tr>
<tr>
<td>25</td>
<td>1/1351</td>
</tr>
<tr>
<td>35</td>
<td>1/384</td>
</tr>
<tr>
<td>40</td>
<td>1/112</td>
</tr>
<tr>
<td>45</td>
<td>1/28</td>
</tr>
<tr>
<td>50</td>
<td>1/6</td>
</tr>
</tbody>
</table>
Cytogenetic findings in DS in Czech republic
1994 - 2001

- Trisomie: 93.30%
- Translokace: 2.49%
- Mosaicismus: 4.21%
Down syndrome - prenatal screening

• I. trimester screening – combined screening
• 10.-14. week of gestation
• Ultrasound
• Nuchal translucency - NT (↑)
• (Absence of nose bone)
• Blood
• PAPP-A (↓)
• free-beta hCG (↑)
• False positive results less than 5%
• Reveals about 95% of fetuses with Down syndrome
• 1/100 – positive – genetic counselling and karyotyping
• 1/100-1/1000 – US and genetic counselling
• 1/1000 – negative - US
Down syndrome - prenatal screening

- II. trimester screening – biochemical screening
- 16.-18. week of gestation
- AFP – alpha-fetoprotein (↓)
- total hCG - chorionic gonadotropin (↑)
- uE3 - unconjugated estriol (↓)

- Fals positive results about 5%

- Reveals about 70% of fetuses with Down syndrome

- 1/250 – positiv
- 1/250-1/350 – border
- 1/350 - negativ
Down syndrome - prenatal screening

- **Ultrasound**
- 10.-14. week
- NT
- NB
- Some congenital malformations
- 20. week
- US
- Congenital malformations
- congenital heart disease
Nuchal Translucency
I. Trimester screening

- Age – 28.8
- Week of gestation 13+2 (US)
- FβhCG 26.66 – 1.09 MoM
- PAPP-A 2.93 – 0.82 MoM
- NT 2.0mm – 1.76 MoM

- Risk for Down syndrome in age 28.8 years – 1/1100

- Combine risk for DS 1/2700

- Negative I. trimester screening
I. Trimester screening

- Age – 33,6
- Week of gestation 12+5 (US)
- FβhCG 113,4 – 3,41 MoM
- PAPP-A 1,86 - 0,55 MoM
- NT 1,6 mm – 1,25 MoM

- Risk for DS in age 33,6 years – 1/550
- Combine risk for DS 1/80
- Positive I. trimester screening
I. Trimester screening

- Age – 33,6
- Week of gestation 12+5 (US)
- FβhCG 113,4 – 3,41 MoM
- PAPP-A 1,86 - 0,55 MoM
- NT 1,6 mm – 1,25 MoM
- Risk for DS in age 33,6 years – 1/550
- Combine risk for DS 1/80
- **Positive I. trimester screening**

**Recommendation**
- Genetic consultation
- Karyotyping of the fetus
- Detailed ultrasound examination of the fetus
II. Trimester screening

- Age – 29.9
- Week of gestation
- 15+1
- AFP 48.0 - 1.66 MoM
- uE3 3.09 – 1.07 MoM
- Total hCG 40.2 – 0.99 MoM

- Risk for DS in age 29.9 years – 1/1000
- Combine risk for DS less then 1/50 000
- Negative II. trimester screening

- Recommendation
- Detailed ultrasound examination of the fetus in 20. week of gestation
II. Trimester screening

- Age – 33,7
- Week of gestation
  - 15+3
- AFP
  - 21,1 – 0,71 MoM
- uE3
  - 1,55 – 0,49 MoM
- Total hCG
  - 35,1 – 0,95 MoM

- Risk for DS in age 33,7 years – 1/540
- Combine risk for DS 1/220
- Positive II. trimester screening

- Recommendation
- Genetic Consultation
- Karyotyping
- Detailed ultrasound examination of the fetus
II. Trimestr screening

- Age – 25,7
- Week of gestation
- 20+5
- AFP 27,6 - 0,50 MoM
- uE3 6,28 – 0,38 MoM
- Total hCG 4,2 – 0,21 MoM
- Risk for DS in age 25,7 years – 1/1300
- Combine risk for DS 1/6300
- Risk for Edwards syndrome 1/3
- Risk for Smith-Lemli-Opitz syndrome 1/65

- Recommendation
- Genetic Consultation
- Fetal karyotyping, DNA of the fetus (SLOS)
- Detailed ultrasound examination of the fetus
- DNA analysis SLOS – both parents
Integrated screening

- Age – 25,8
- Week of gestation
  - 1. 12+6 (US)
  - 2. 15+6
- AFP 29,8 – 0,97 MoM
- uE3 3,45 – 0,96 MoM
- Total hCG 48,5 – 1,48 MOM
- PAPP-A 4,1 – 1,16 MOM
- NT 1,3 mm – 1,01 MoM
- Risk for DS in age 25,8 years – 1/1300
- Combine risk for DS 1/15 000
- Negative integrated screening

Recommendation
- Detailed ultrasound examination of the fetus in 20. week of gestation
Non-invasive prenatal testing (NIPT)

- examination of free fetal DNA in maternal plasma
- performed outside the Czech Republic
- reliability over 98%
Edwards syndrome

- 47,XX(XY),+18
- 1/5000-10 000 in newborns, 1/45 SA
- gyneokotropie 4:1
- SA - 95%, death before 1 year mostly

- hypotrophy, atypical hands and feets, profil, prominent nose, small chin, congenital defects
Edwards syndrome

- 1:5000
- IUGR, hyopotrophie
- microcephhalie
- dolichocephhalie
- Cleft palate
- Down set ears
- micromandibula
- Hands, feets
- Other cong. malformations
Patau syndrome

- 47,XX(XY),+13
- 1/5000-10 000 in newborns, 1/90 SA
- 95% SA
- death before 1 year mostly

- cleft lip and palate bilateral, congenital defects (CNS, eyes, postaxial hexadactily...)
Patau syndrome

- Microcephalie
- Trigonocephalie
- skin defects in the hairy part calva
- congenital defects of the brain (holoprosencephalie, arinencephalie)
- micro-anophthalmia
- Cleft lip, palate hexadactilie
- heart defects
Turner syndrome

- 45,X (in about 55%), mosaicism, structural abnormalities of X chromosome
- 1/2500 newborn girls, min. 95% SA
- Prenat.- hydrops foetus, hygroma coli

- Postnatal lymphedema on feet, pterygium coli, congenital heart defect coarctation of aorta, small stature, other congenital defects, hypogenitalismus, hypergonadotropins, sterility-infertility
Turner syndrome 45,X

- 1:2000
- hygroma colli
- hydrops
- Low weight in newborns
- Lymfoedema
- Pterygia
- Cubiti valgi
- Aortal stenosis
- Small statue
- Sterility
Klinefelter syndrome

• 47,XXY
• relatively frequent 1/600-1000 liveborn males
• tall stature
• hypogonadism, gynekomastia
• sterility, infertility
Klinefelter syndrome 47,XXY

- Testicules de petit volume
- Atrophie tubulaire
- Gynécomastie
- Grande Taille
- Grande envergure
- Rapport SS/ SI diminué
- Difficultés Scolaires
- FSH ↗ et LH ↗, testo svt basse
- 47, XXY
Others gonosome abnormalities

• 47,XXX
• 47,XYY
• 48,XXXX
• 48,XXYY
Structural chromosomal aberrations

- deletion or a duplication of the genetic material of any chromosome, atypical structure - side by side to get the genetic material, which there normally is not - the effect of positional
- partial-partial deletions
- partial trisomy
- inversions, insertions, duplications...
Types of mutation

Deletion

Duplication

Inversion

Insertion

Chromosome 20

Chromosome 4

Translocation

Chromosome 20

Derivative Chromosome 20

Chromosome 4

Derivative Chromosome 4
Wolf-Hirshorn syndrome
46,XX(XY),4p-

• severe mental retardation
• typical craniofacial dysmorphia - hypertelorism, pear nose, carp mouth,
• pre-and postnatal growth retardation,
• failure to thrive
• other associated developmental defects - heart, urogenital tract ...
Cri du chat syndrome
46,XX(XY),5p-

• anomalies of the larynx causes the characteristic cry of a similar feline meow (only in infancy)
• low birth weight and length
• mental retardation, short stature, failure to thrive, small moon shaped face, the position antimongoloid eye slits, mikrocephalalie
• Other malformations and birth defects
Cri du chat  46,XX(XY),5p-

• 1:50 000
• Typically cri in newborns
• laryngomalacie
• antimongoloid
• epicanthi
• hypotonie
• hypotrofie
Mikrocytogenetic
Molekular cytogenetic

- FISH (fluorescence in situ hybridisation), M-FISH, SKY (spektral karyotyping), CGH (komparativ genom hybridisation), MLPA
- mikrodeletions or mikroduplications, marker chromosomes, complex rearrangements, oncology – oncocytogenetics, fast prenatal diagnostics …
- fast methods (possible for prenatal dg)
- metafase and intesfase examination
Examples of different types of fluorescence in situ hybridisation (FISH) probes

Gene-specific probe

Centromeric probe

Telomeric probe

Chromosome-painting probe

Repetitive-sequence probes
M-FISH (multicolor)
Spektral karyotyping (SKY)
Comparativ genom hybridisation
MLPA
Multiplex Ligation-Dependent Probe Amplification
Array CGH

- DNA mikroarray
- Chip technology
Microdeletions

• Di George syndrome (del 22q11)

• Prader-Willi / Angelman syndrome (del15q11-13)

• Williams Beuren syndrome (del7q11.23)
Syndrom Di George

- Velo – Kardio- Facial syndrome
- CATCH 22
- Congenital heart disease – conotruncal, craniofacial dysmorphism, thymus aplasie, immunodeficiency, hypoparathyroidismus
DiGeorge syndrom

22q11

del 22q11
DiGeorge syndrom

del 22q11
Williams - Beuren syndrome

• del 7q11.23

• Facial dysmorfie - Elfin face, congenital heart disease, aortal or pulmonal stenosis, hypokalcemie, small statue, MR, hernie,...
Prader-Willi syndrome

- Hypotonia, hypotrophy in small children
- PMR, small statue, obesity, hyperfagie, akromikrie, hypogonadismus
- mikrodeletion15q11-12 paternal
Angelman syndrome

- Severe mental retardation
- Epilepsie
- Laughter
- Severely delayed speech development
- Mikrodeletion 15q11-12 mat
The telomeres

Rearrangement in about 6-8% children with mental retardation with or without congenital defect (FISH, HR-CGH, MLPA)
Secondary prevention of genetic

• The procedures in pregnancy - prenatal diagnosis and early postnatal diagnosis
Prenatal diagnosis

• Non invasive methods- screening

• Invasive methods
  • CVS – after the 10. week of gestation
  • AMC – 15.-18. week of gestation
  • Cordocentesis – after the 20. week of gestation
Indications for prenatal examination / genetic counselling

- US screening – congenital defects
- Positive prenatal screening for chromosomal abnormalities
- Known chromosomal abnormality (de novo finding in previous child, structural change in parents)
- Advanced maternal age (35/38 years)
- Family history of known conditions for which diagnosis is possible (DNA analysis)
Prenatal screening (CR)

- Ultrasound (12. - 20. - 33. week)
- Ultrasound 20. week – cong. defect
- Ultrasound 20-22. week – cong. heart defect
- 10-14. week of gestation
- 16.-18. week of gestation
- AFP, hCG, uE3
Prenatal diagnosis results

- CVS – karyotype – about 5 days
- AMC – karyotype – about 14-21 days
- DNA analysis (monogen diseases)
  - About 5-15 days
- DNA from amniocytes after cultivation - exclusion contamination by maternal tissues
Prenatal analysis of most frequent aneuploidias

QF PCR

• Examination of the most common numerical changes in chromosomes 13, 18, 21, X and Y

• The result for 24-48 hours
Preimplantation Genetic Diagnostics
Preimplantation Genetic Diagnostics

- IVF – assisted reproduction

- Preimplantation genetic screening
- aneuploidias - array- CGH, chip technology
- FISH (13,18,21,X,Y, 15,16,22)

- Preimplantation Genetic Diagnostics
- Structural chromososmal aberations
- (parents are carries of balanced rearangements)
- Monogenic diseases (known in family history)
PG Diagnostic

X

PG Screening

- PG Diagnostic
- high genetic risk
- Structural chromosomal aberration in parents
- Monogen diseases

- PG Screening
- aneuploidies
PGD – day 5, array-CGH