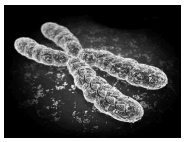
MEDICINE, 2015.



ANTENATAL DIAGNOSTICS
FETAL ANOMALIES

prof. Damir Roje

BE CAREFUL!

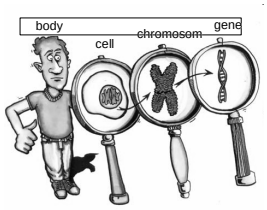
Antenatal fetal malformation diagnostics makes sence if ….

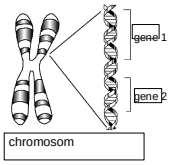
- maior malformations – indication for termination of pregnancy
- maior malformations – that are operabile immediately after birth
- minor malformations – not resonable reason for pregnancy terminaton, but could be connected in some syndromes
- Chromosomopathies linked malformations (yet to be proven) if that chromosomal abnormalitie presents indication for termination of pregnancy
- Pregnant woman "wants to know" and has right to know if her baby has any malformation that coulud be diagnosed throughout pregnancy

PAZI

- anomalies and chromosomopaties are not the same, although overlap partialy
- genetic counseling "covers" all the genetic and hereditary diseases, not only chromosomal anomalies, and not only (structural) anomalies

CHROMOSOMOPATIES AND GENOPATHIES ARE NOT THE SAME !!!





BE CAREFUL!

Genetic defects can be detected prenatally, but not by screening of all pregnant women but within the high-risk families

CHROMOSOMOPATIES ARE NOT THE SYNONYM WITH ALL FETAL ANOMALIEIS

(different chromosomopaties can be connected with different anomalies in different and not always the same combinations)

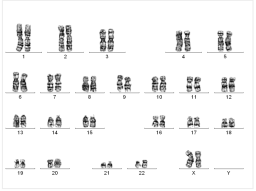
Teratology
science on the causes, mechanisms and manifestations of developmental abnormalities of structural or functional nature.

CHROMOSOMOPATIES

- anomalies of number and structure of chromosomes

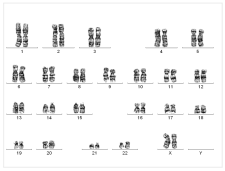
HUMAN KARYOGRAM

♀ 46, xx ♂ 46, xy



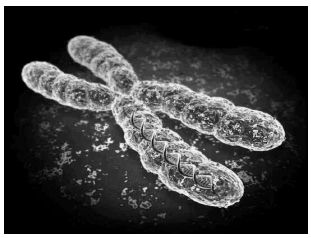
CHROMOSOMOPATHIES

- anomalies of structure of the chromosome



➢ *"cri du chat" syndrom (4. chromosome deletion)*

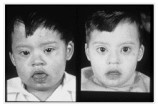
CHROMOSOMOPATHIES

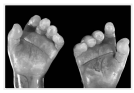


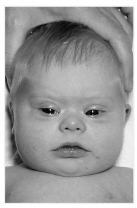
➢ *ANOMALIES OF CHROMOSOME NUMBER:*
⇨one chromosome ⇨ trisomy or monosomy
⇨ Complete shromosome set ⇨ polyploidy

CHROMOSOMOPATHIES
Sy. Down ⇨ Trisomy 21. (47, XY, +21)

Langdon Down 1828-1896







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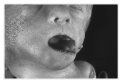
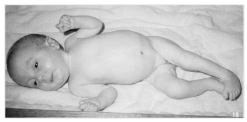
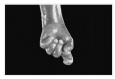
CHROMOSOMOPATHIES
Sy. Edwards ⇨ trisomy 18. 47, XY, +18)







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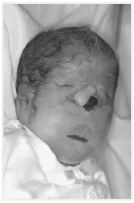
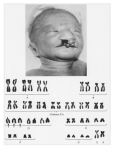
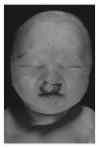
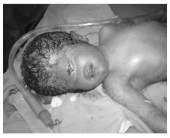
⇨ Complete shromosome set ⇨ polyploidy

CHROMOSOMOPATHIES
Sy. Patau ⇨ trisomy 13. (47, XY, +13)









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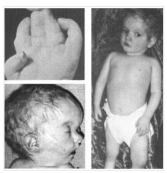
CHROMOSOMOPATHIES ⇨ tryploidy (69, XXX)



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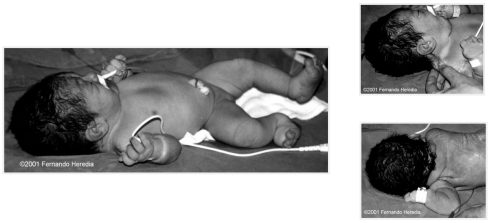
CHROMOSOMOPATHIES – sex chromosomes
Sy. Turner ⇨ X monosomy (45, X0)



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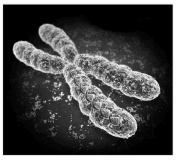


- chromosomal abnormalities that present indication for termination of pregnancy
- Possible connection between structural fetal malformations or fetal growth imaparements with chromosomopathies

- Sy. Down ~ 1:650
- Sy. Edwards ~ 1:5000
- Sy. Patau ~ 1:5000
- delecije, translokacij

- Sy. Turner (45, X0) 1:2500 ⇨ *90% misscariage*
- Sy. Klinerfertner (47, XXY) 1:500-1000 ⇨ *isn't indication for termination*
- (47, XYY) 1:500-1000 ⇨ *isn't indication for termination*
- (47, XXX) 1:1200 ⇨ *isn't indication for termination*

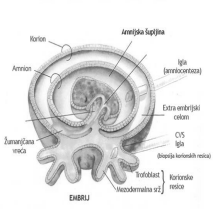
HOW TO BE SURE IN FETAL CHROMOSOMOPATHIES?

- *CITOGENETICS !!!!*
- *Amniotic fluid or some other fetal byologic materijal*
- *Invasive procedures are necessary!!!*

HOW TO BE SURE IN FETAL CHROMOSOMOPATHIES?

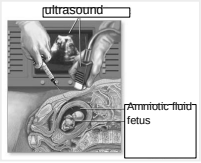
- amnicentesis
- chordocentesis
- chorionic villus sampling
- placental biopsy
- *fetal cells in mothers circulation*

- *Be careful: fetal DNA in mothers circulation*



AMNIOCENTESIS

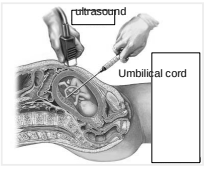
- *sample is the amniotic fluid*
- *16th to 19th week of pregnancy*
- *culture of fetal amniotic cells – has to be done!*
- *Results in three weeks*
- *Preliminary findings possibe in 2-3 days*
COMPLICATIONS: miscarriage ~ 0.5-1%



CHORDOCENTESIS

- *Semple is fetal blood (2-3 ml heparinized blood)*
- *necessary to determining fetal Hbg (pollution - the mother's blood)*
- *Analysis: karyogram, biochemistry, coagulogram …*
- *Detection of viral infections, ...*
- *Results in two to three days*

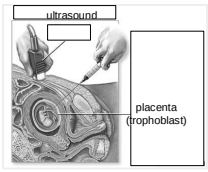
COMPLICATIONS: just over 1%



CHORION VILLUS SAMPLING

CVS: biopsy of the placenta in the first trimester
not before 8 weeks
no cell cultures, results in 2-3 days
complications similar to the early amniocentesis

Placenta: *a biopsy of the placenta in the second or third quarter*
no cell cultures, finding ~ 2-3 days
complications generally rare
LATE FOR CHROMOSOMOPATIES DIAGNOSIS!



FETAL CELLS IN MOTHER'S CIRCULATION

every millionth erythrocyte in the mother's blood is of fetal origin

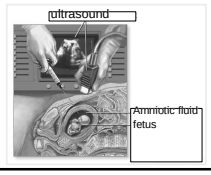
fetal red blood cells have a nucleus (prerequisite karyogram)

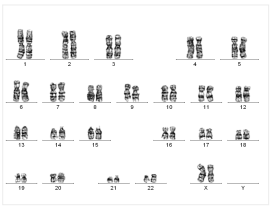
CAREFUL with *free fetal DNA in maternal blood* - SEARCH FOR THE FUTURE!

AMNIOCENTESIS IS GOLD STANDARD

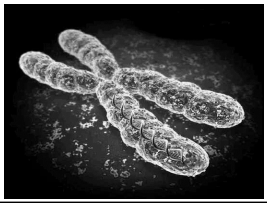
BENEFITS
- Easy to perform
- ⇩ complications

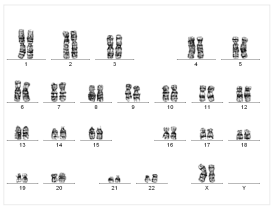
PROBLEM
- Not before 16th week
- Result in 2-3 weeks

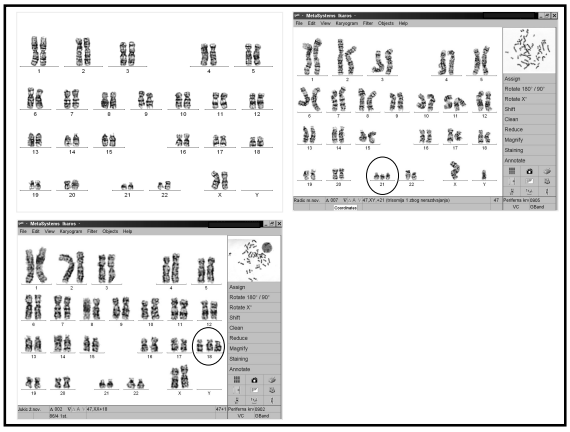


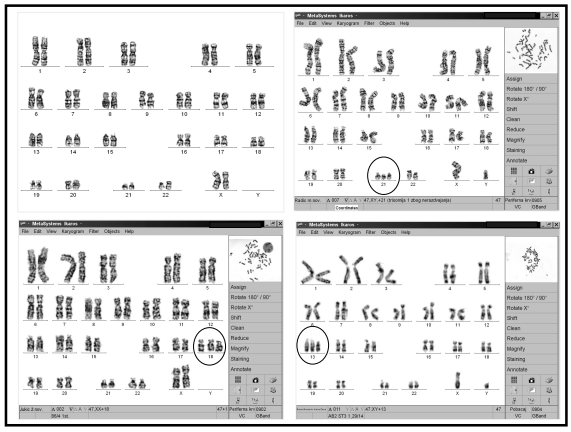


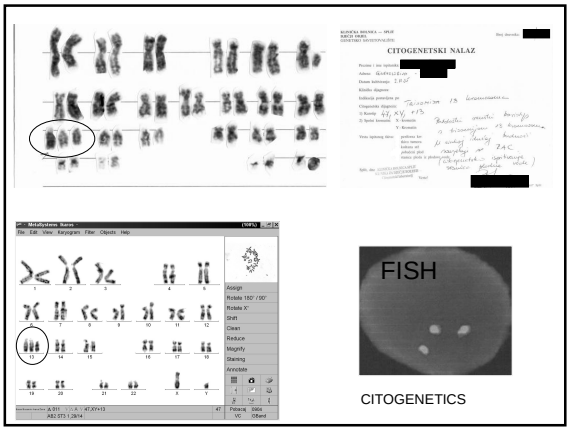
Normal female karyogram
46, XX





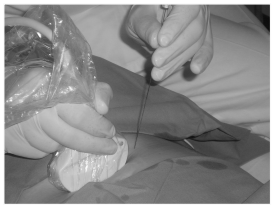






CITOGENETICS

WHOM TO OFFER ACZ?



WHOM TO OFFER ACZ?

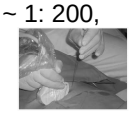
- **TO EVERY pregnant women in which is the probability of fetal chromosomopathies greater than the risk of fatal complications of the procedure ....**
- If she wants it after consultations with her PARTNER and after being informed of the procedure purpose (termination of pregnancy in case of pathological finding)
- **After you explain her clearly:**
- What can be obtained by searching?
- What can not be obtained by searching (and she maybe thinks that is possible) ?
- What can search lose?

WHOM TO OFFER ACZ?

- What she can get?
- Safe and unambiguous answer about fetal karyogram
- What she can't get?
- answer to the question "is everything all right" and the security that a child has no abnormalities
- What she can lose ?
- 1: ~ 200 ACZ' performances ⇨ miscarriage (probable / possible) as a complication of procedure

WHOM TO OFFER ACZ?

- WHEREAS, THE ESTIMATED PROCEDURE RISK IS ~ 1: 200 ...
- .... it makes sense to offer ACZ to every pregnant women in which is the probability of fetal chromosomal greater than ~ 1: 200, and she wants it!



How to calculate the individual risk? (... and find the one with the risk> 1: 200)

BASICS:

- Every woman has a risk!
- "*A priori risk*" is dependent on the age of the parents and the gestational age
- individual risk is calculated by increasing the basic risk with "additional factors"

How to calculate the individual risk? (... and find the one with the risk> 1: 200)

SCREENING

How to calculate the individual risk? (... and find the one with the risk> 1: 200)

Good screening method is:

- simple
- cheap
- harmless
- repeatable
- specificity
- sensitivity
- without side effects and additional risks

How to calculate the individual risk? (... and find the one with the risk> 1: 200)

SCREENING METHODS:

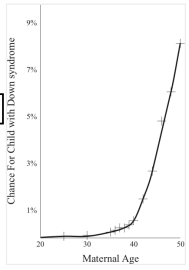
- Maternal age
- family history
- previous pregnancies history
- ultrasound
- biochemistry

MATERNAL AGE

20 god. ⇨ 1:1527
30 god. ⇨ 1:895
35 god. ⇨ 1:356

ACZ RISK IS ~1:200 (0,5%)!

37 god. ⇨ 1:218
38 god. ⇨ 1:167
40 god. ⇨ 1:97
42 god. ⇨ 1:55



How to calculate the individual risk?
(... and find the one with the risk> 1: 200)

SCREENING METHODS:

- Maternal age – 30%
- family history - rarely
- previous pregnancies history - rarely
- ultrasound
- biochemistry

70%

ULTRASOUND AND BIOCHEMISTRY IN SCREENING FOR CHROMOSOMOPATHIES

phase No.1.
Second trimester




ULTRASOUND AND BIOCHEMISTRY;
phase 1. – second trimester

BIOCHEMISTRY second trimester:

- 1984. AFP (alpha feto protein)
- *double test* ⇨ AFP, free ßHCG
- *triple test* ⇨ AFP, slobodni ßHCG, E3 (estriol)
- *quadriple test* ⇨ AFP, ßHCG, E3, inhibin A

ULTRASOUND AND BIOCHEMISTRY;
phase 1. – second trimester

BIOCHEMISTRY second trimester :

- AFP
  * detection rate: ~ 20%
- double test
  * detection rate : ~ 50-60%
- triple test
  * detection rate: ~ 60-70%
- quadruipet test
  * detection rate: ~ 75-80%

☹

* 5% false positive !!!

ULTRASOUND IN FETAL
CHROMOSOMOPATHY SCREENING

ULTRASOUND - secnod trimester – “soft markers” (low likelihood ratio)

- kratak femur i/ili druge duge kosti; anomalije prstiju
- hiperehogeno crijevo
- strukturne anomalije lica
- cista korioidnog pleksusa
- cholоprosencefalija
- nuhalni nabor
- hipoplazija nosa, micrognatia
- arteria umbilicalis una
- pijelektazije
- hiperehogena žarišta u srcu
- omphalocele
- IUGR
- multiple anomalije
- .....

* Detection rate: 50-70%

☹

* 5% false positive

First trimester

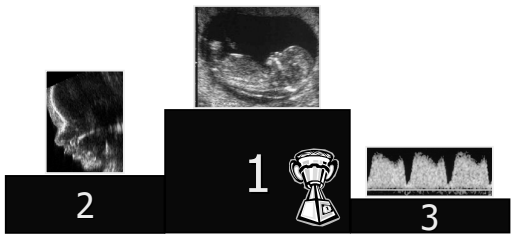
BIOCHEMISTRY first trimester:

- PAPP-A
  * detection rate: 52% *(Benn PA. Clin Chim Acta 2002.)*
- free ßHCG
  * detection rate : 42% *(Cuckle HS, van Lith JM. Prenat Diagn 1999.)*
- PAPP-A+ free ßHCG
  * detection rate : 65% *(Benn PA. Clin Chim Acta 2002.)*

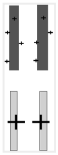
II. Trimester triple test: * detection rate: *60-70%*

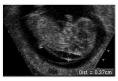
* 5% false positive

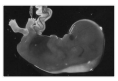
ULTRASOUND IN FIRST TRIMESTER

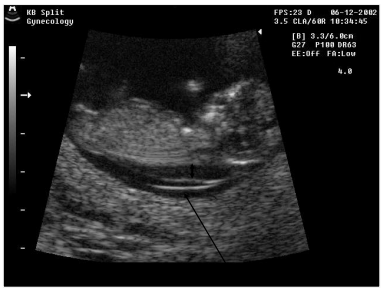


Nuchal translucency - NT



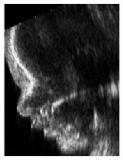






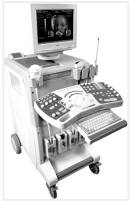
NASAL BONE – US
Chromosomopathy screening

- 1% of all Caucasians and 10% of all Afroamericans
- Sy. Down: nasal bone ⇩ in 60-70%
- Sy. Edwards: nasal bone in ⇩ 50%
- Sy. Patau: nasal bone ⇩ in 30%



Nicolaides KH. Am J Obstet Gynecol 2004.

US & BIOCHEMISTRY AS THE FIRST TRIMESTER COMBINATION



COMBINED FIRST TRIMESTER SCREENING
(11 – 13$^{+6/7}$ tj.)

Mothernal age (years)

US: NT + (*sometimes) nasal bone*

\+ Biochemistry: free ßHCG + PAPP-A

*DETECTION RATE: 85-90%

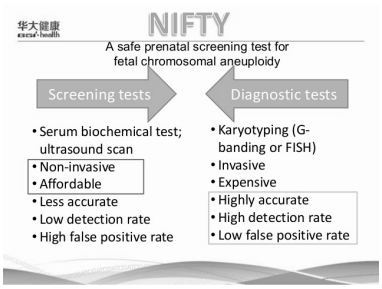
Nicolaides KH. Am J Obstet Gynecol 2004. (meta-analysis N=40 000)

11. weeks ⇨ *detection rate: 82%
12. weeks ⇨ *detection rate: 85%
13. weeks ⇨ *detection rate: 87%

Malone FD, et al. N Engl J Med 2005

* 5% false positive

Fetal DNA - peripheral maternal blood



Thank you …