

# Fetal Diagnostic Centre



# Practical Aspects of Down's Syndrome Screening – General Introduction of Combined Test

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*1:Magzati Diagnosztikai Központ*

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# Current practice in Hungary

- NT-measurement /11<sup>+0</sup> - 13<sup>+6</sup> gestational week/
- AFP-measurement /maternal blood, 16<sup>th</sup> gest. week/

In cases of low AFP-value, positive family history, US-signs, or maternal age over 35 years



Genetic counselling is offered to decide about invasive fetal sampling for chromosome-analysis.

# The risk of Down-syndrome in relation of maternal age

Maternal age	Risk of Down-syndrome		Maternal age	Risk of Down-syndrome		Maternal age	Risk of Down-syndrome	
	Rate	%		Rate	%		Rate	%
<b>&lt; 25</b>	<b>1:1500</b>	0.066	<b>33</b>	<b>1:570</b>	0.175	<b>42</b>	<b>1:65</b>	1.54
<b>25</b>	<b>1:1350</b>	0.074	<b>34</b>	<b>1:470</b>	0.212	<b>43</b>	<b>1:50</b>	2.00
<b>26</b>	<b>1:1300</b>	0.077	<b>35</b>	<b>1:380</b>	0.263	<b>44</b>	<b>1:35</b>	2.86
<b>27</b>	<b>1:1200</b>	0.083	<b>36</b>	<b>1:310</b>	0.322	<b>45</b>	<b>1:30</b>	3.33
<b>28</b>	<b>1:1100</b>	0.091	<b>37</b>	<b>1:240</b>	0.416	<b>46</b>	<b>1:20</b>	5.00
<b>29</b>	<b>1:1000</b>	0.100	<b>38</b>	<b>1:190</b>	0.526	<b>47</b>	<b>1:15</b>	6.66
<b>30</b>	<b>1:910</b>	0.110	<b>39</b>	<b>1:150</b>	0.666	<b>48</b>	<b>1:11</b>	9.09
<b>31</b>	<b>1:800</b>	0.125	<b>40</b>	<b>1:110</b>	0.909	<b>49</b>	<b>1:8</b>	12.50
<b>32</b>	<b>1:680</b>	0.147	<b>41</b>	<b>1:85</b>	1.17	<b>50</b>	<b>1:6</b>	16.66

# Results of current Hungarian pregnant-care protocol /HCAR\* 2005/

- All Down syndrome fetuses: 152
- The number of prenatally diagnosed Down-sy. fetuses: 65
- Not diagnosed Down-sy. fetuses: 87
- *DETECTION RATE:  $65/152 = 42,8\%$*

/Live births are appr. 100.000 per year/

\* Hungarian Congenital Abnormality Registry

# Results of current Hungarian pregnant-care protocol /HCAR 2006/1

- All Down syndrome fetuses: 171
- Number of diagnosed Down-sy-s fetuses: 96
- Not diagnosed Down-sy. fetuses: 77
- *DETECTION RATE: 96/171 = 56,14 %*
- All live births: appr. 100000
- Number of performed chromosome-analyses: 7200\*
- FPR/spec.: 7200/100,000 = *7,2%*
- Complication: *1% risk of miscarriage*

\* National Health Insurance /OEP/

# Results of current Hungarian pregnant-care protocol /HCAR 2006/2

44% of affected pregnancies happened among pregnant women older, than 35 years.

About 56% of affected pregnancies occur in women under 35 years.

Age over 35 years	78 % is detected prenatally
Age under 35 years	44.5 % is detected prenatally

# Realised DR in relation of maternal age

Maternal age	Undetected affected pregnancies	Detected affected pregnancies	Realised DR in given age-groups
under 35 years	46	37	44,5%
35-37 years	7	21	75%
38-39 years	4	16	80%
over 40 years	6	23	80%

- maternal age is unknown in 13 cases
- above 35 years of age the DR is 78% in contrast with expected 100% because of the age-limit
- above 38 years of age the DR is the same 80%.



# Facilities

- **Combined-test:** NT /US/, PAPP-A,  $\beta$ -hCG  
/11<sup>th</sup>-14<sup>th</sup> gestational week/
- **Quadruple-test:** AFP,  $\beta$ -hCG, uE3, Inhibin-A  
/15<sup>th</sup>-22<sup>nd</sup> week/
- **Integrated-test:** NT/US/, PAPP-A  
/ 11<sup>th</sup>-14<sup>th</sup> week/  
/2-steps/ AFP,  $\beta$ -hCG, uE3, Inhibin-A  
/15<sup>th</sup>-22<sup>nd</sup> week/

# Detection rate with 5% FPR

in practice

- Maternal age+NT+AFP: 73% 56%/7,2%
- Quadruple-test: 80%
- Combined-test: 86%
- Integrated-test: 94% 86%/1%

# The average risk-values of tests

Test with 1:250 cut-off	Average positive result of affected pregnancies	Average negative result of unaffected pregnancies
<b>Quadruple-test</b> /80%/	<b>1:35</b>	<b>1:7,000</b>
<b>Combined-test</b> /86%/	<b>1:10</b>	<b>1:2,300</b>
<b>Integrated-test</b> /94%/	<b>1:3</b>	<b>1:27,000</b>

# The results of Fetal Diagnostic Centre by Quadruple-test



- From 1999 to 2008 we performed 3388 tests
- Used risk cut-off is 1:250
- The average age of women is 32 years
- 28% of the pregnant women were over 35 years of age

	Realised result /1:250/	Expected result /1:250/
DR	66%	86%
FPR	9,2%	7,5%

# The results of Fetal Diagnostic Centre by Integrated-test



- From 2003 to March 2008 we performed 3065 tests
- used risk cut-off 1:150
- The average age of women 33 years
- 37% of the pregnant women were above 35 years of age

	Realised result /1:150/	Expected result /1:150/	Expected result /1:250/
DR	100%	89%	92%
FPR	2,5%	2,6%	3,9%

**Which test is appropriate for screening large number of pregnant women ?**



## **Combined-test:**

- Simple to perform
- Early result
- Simple to complete

## **Integrated-test:**

- Most exact
- 2 steps

## **Quadraple-test:**

- Lately result
- Low detection rate

# Comparison

## Protocol

- All DR: 56,1%
- Over 35 years DR: 75%
- Over 38 years DR: 80%
- Over 40 years DR: 80%
- Under 35 years DR: 44,5%
  
- All FPR: 11% /7,2%/
- Over 35 years FPR: 100%
  
- Under 35 years FPR: 1%

## Combined-test

- All DR: 86%  
/NT: by method of Nikolaides/
- Over 35 years DR: 87%
- Over 40 years DR: 95%
- Under 35 years DR: 70%
  
- All FPR: 4-5%
- Over 35 years FPR:11%
- Over 40 years FPR: 27%
- Under 35 years FPR: 2%



# The general introduction of Combined-test



- Financing by: Sejtbank Ltd. /Cryo-Save/:  
The test is offered free of charge.
- We complete the given NT-value with measurement of  $\beta$ -hCG and PAPP-A, additionally estimating risk collaborated with Wolfson Institute.
- We perform the screening in the regional antenatal care centers, also in private sector.
- Beginning of program: May, 2008
- We've performed 1700 tests until now.

# Potential problems

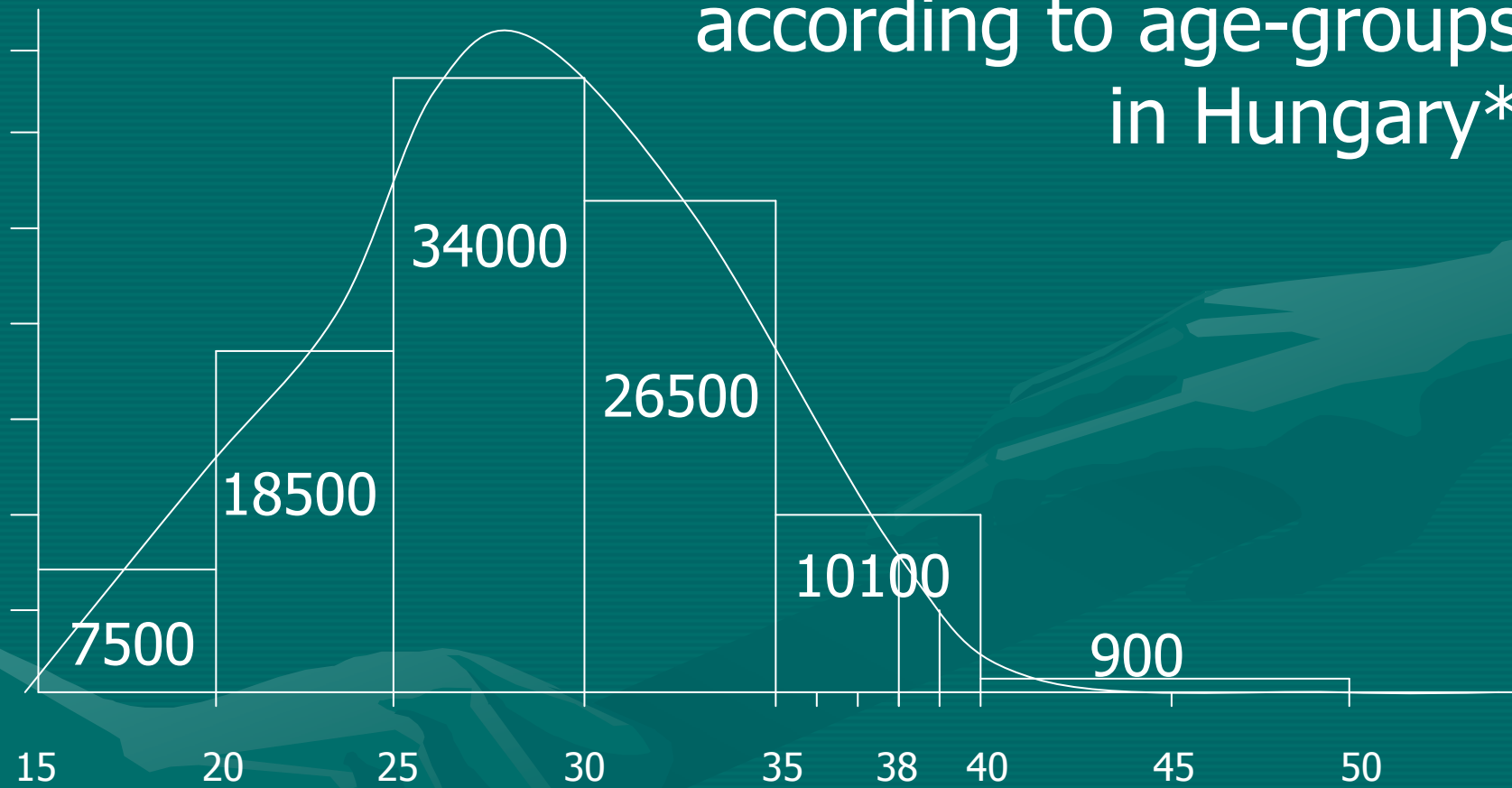
- Deficiency of NT-measurement in certain regions of Hungary
- The problem of maternal age-limit
- Overburdened genetic centers

# Solution

- Strict quality control of NT-measurement
- Organised trainings for appropriate NT-measurement in Hungary,
- To select the high-risk pregnancies by complex screening methods
- To decrease the load of overburdened genetic centers.

# Distribution of birth-number according to age-groups in Hungary\*

Births/year



\*Statistical Annual

Maternal age

# Number of chromosome-analyses

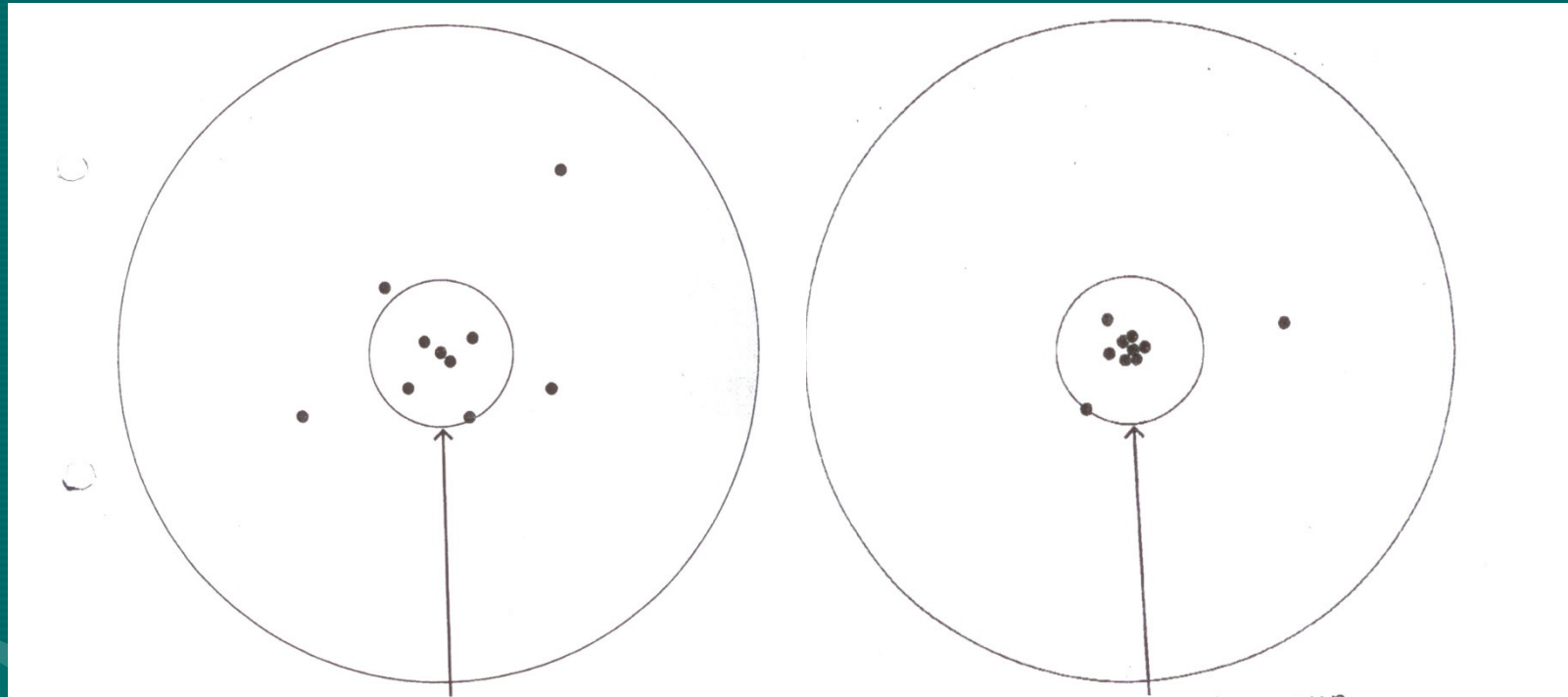
Protocol-2006	<b>7200</b>
2007	5800
Combined-test /without maternal age-limit/	About 5000 /FPR:5%/
Combined-test + chromosome-analyses over 35 years	$7200 + 1800 / 88000 \times 0.02 / = 9000$ /FPR is 2% in the group of under 35 years of age/
Combined-test + chromosome-analyses over 38 years	$3000 + 4800 = \mathbf{7800}$

# Conclusion

## Mass-screening with Combined-test

- Higher detection rate of Down's syndrome affected pregnancies (56% - 85%),
- The number of invasive diagnostic test could be reduced.

# Thank you for your attention!



**2006, Hungary**

**Combined-test**

## Recommendations:

If we define the maternal-age limit, as 38 years, similarly the recommendation of Nicolaides\*,

- we could reach higher detection rate, because of the higher rate of participation of chromosomal-analyses, and
- the detection rate would rise in the group under 38 years of age,
- we wouldn't lose the cases with other chromosomal-defects, which are happened in 1% above 40 years of age,/Lancet-2005/
- the number of chromosomal-analyses would decrease in group between 35-38 years, so we could equilibrate the higher number of performed chromosomal-analyses in the group under 35 years.

\* K.Nicolaides,FetalMedicine Foundation: 11-13+6 weeks scan book 12th.page