Rigshospitalet
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Overview of Noninvasive Fetal RhD Genotyping

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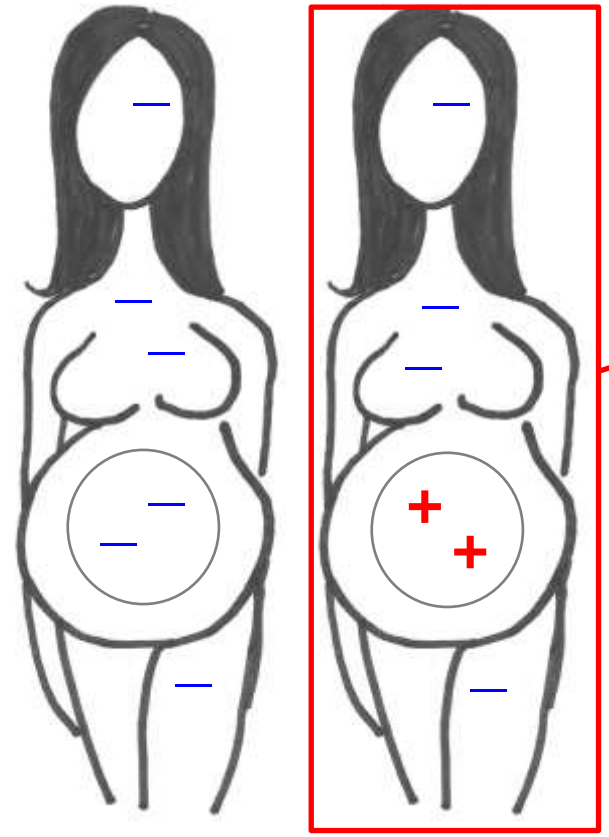
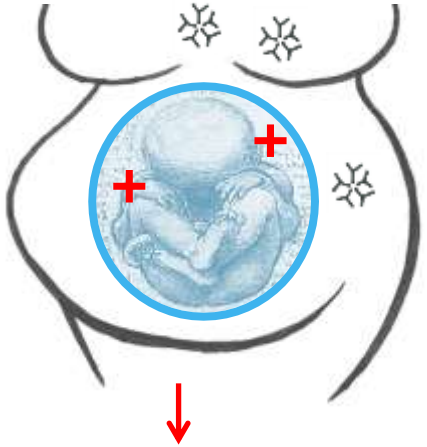
3rd International Meeting on Cell-Free DNA, cfDNA2017

RhD negative pregnant women

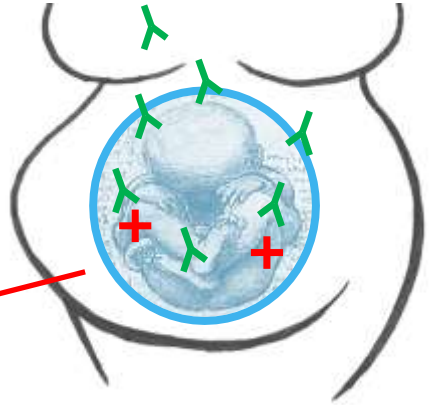


Prophylaxis

Risk of becomming immunized



If immunized, then risk of HDFN



HDFN

HDFN = Hemolytic Disease of the Fetus and Newborn

Noninvasive Fetal RhD Genotyping

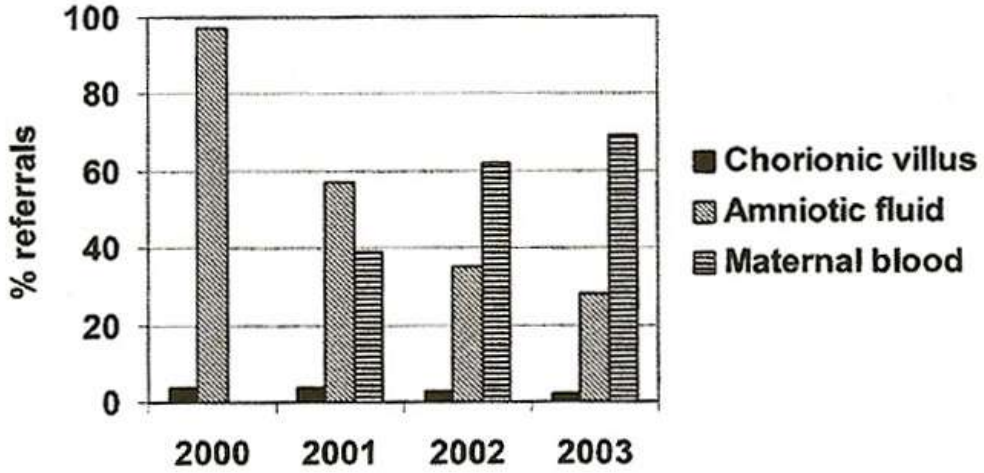
Immunized women

Purpose:
To predict risk of HDFN

Non-immunized women

Purpose:
To guide use of prophylaxis

Noninvasive Fetal RhD Genotyping



Finning K, Martin P, Daniels G. *A clinical service in the UK to predict fetal Rh (Rhesus) D blood group using free fetal DNA in maternal plasma.* Ann N Y Acad Sci 2004; 1022:119-23.

Overview of large-scale studies

TABLE 1. Results from antenatal *RHD* screening

Reference	Samples (n)	Gestational weeks (median)	*RHD* exons	Sensitivity (%)	False-negative results[a]	Specificity (%)	False-positive results[a]
Trials							
van der Schoot *et al.*, 2006	1,257	30	7	99.6	3		
Finning *et al.*, 2008	1,869	8–38 (28)	5, 7	99.7	3	98	14
Müller *et al.*, 2008	1,022	6–32 (25)	5, 7	99.7	2	99.2	3
Chitty *et al.*, 2014	4,913	7–24	5, 7	99.3[b]	19	94.9	18
Routine							
Clausen *et al.*, 2012[c]	2,312	25	5, 7; 7, 10; or 5, 10	99.9	2	99.3	6
Wikman *et al.*, 2012	3,291	8–40	4	98.9[c]	23	98.8	14
Clausen *et al.*, 2014	12,688	25	5, 7; 7, 10; or 5, 10	99.9	11	99.1	41
Soothill *et al.*, 2014	502	15–17	5, 7	100	0	99.4	1
Haimila *et al.*, 2015[e]	4,637	24–26	5, 7	99.97	1	99.8	3
de Haas *et al.*, 2016	25,789	27	5, 7	99.94	9	97.7	225

[a]Compared to results from cord blood typing.
[b]The sensitivity reached >99.8% at gestational week 11, with only 3 false-negative results among 4,048 samples.
[c]The data from Clausen *et al.*, 2012 are included in the data from Clausen *et al.*, 2014.
[d]The sensitivity reached 99.3% at gestational week 10.
[e]Unpublished.

Sensitivity of fetal *RHD* screening for safe guidance of targeted anti-D immunoglobulin prophylaxis: prospective cohort study of a nationwide programme in the Netherlands

Masja de Haas,[1,2,3] Florentine F Thurik,[1,4] Catharina P B van der Ploeg,[5] Barbera Veldhuisen,[1,3] Hoang Hirschberg,[6] Aicha Ait Soussan,[1] Heleen Woortmeijer,[3] Frithjofna Abbink,[7] Godelieve C M L Page-Christiaens,[4] Peter G Scheffer,[4] C Ellen van der Schoot[1]

ABSTRACT

OBJECTIVE

To determine the accuracy of non-invasive fetal testing for the *RHD* gene in week 27 of pregnancy as part of an antenatal screening programme to restrict anti-D immunoglobulin use to women carrying a child positive for *RHD*.

DESIGN

Prospectively monitoring of fetal *RHD* testing accuracy compared with serological cord blood typing on introduction of the test. Fetal *RHD* testing was performed with a duplex real time quantitative polymerase chain reaction, with cell-free fetal DNA isolated from 1 mL of maternal plasma The study period

detection of fetal *RHD* was 99.94% (95% confidence interval 99.89% to 99.97%) and specificity was 97.74% (97.43% to 98.02%). Nine false negative results for fetal *RHD* testing were registered (0.03%, 95% confidence interval 0.01% to 0.06%). In two cases these were due to technical failures. False positive fetal *RHD* testing results were registered for 225 samples (0.87%, 0.76% to 0.99%). Weak RhD expression was shown in 22 of these cases, justifying anti-D immunoglobulin use. The negative and positive predictive values were 99.91% (95% confidence interval 99.82% to 99.95%) and 98.60% (98.40% to 98.77%), respectively. More than 98% of the women participated in the screening programme.

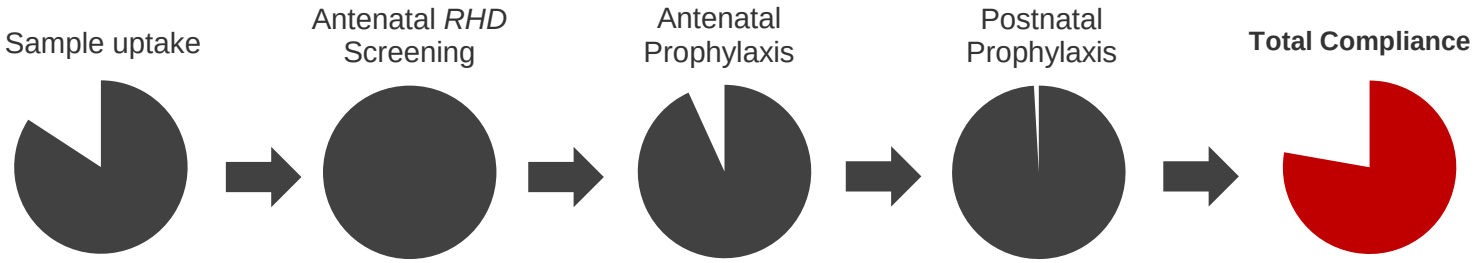
de Haas *et al*. BMJ 2016; 355: i5789.

Noninvasive Fetal RhD Genotyping

- Comments
  - We should do targeted antenatal prophylaxis
  - Compliance is important

Compliance

6-18 months after Danish program launch in 2010



Clausen *et al*. Prenatal Diagnosis 2014; **34**: 1000-5.

Noninvasive Fetal RhD Genotyping

- Comments
  - We should do targeted antenatal prophylaxis
  - Compliance is important
  - External Quality Assurance (EQA)

External Quality Assurance

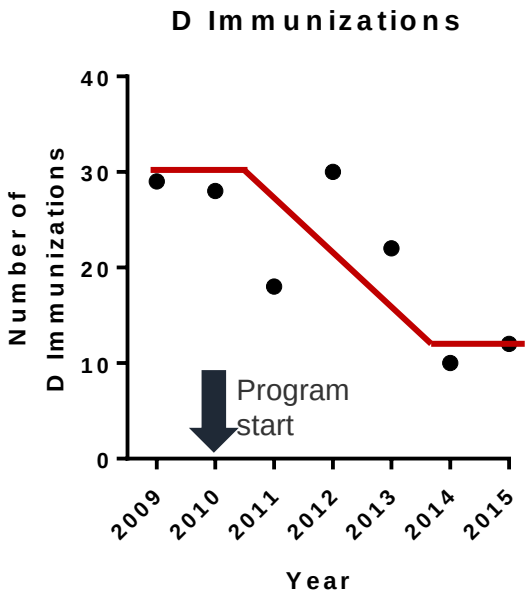
- EQA 2016 completed[1]
  - 22 laboratories participated from 15 different countries
- Expected workshop in September 2017 (EQA 2017)
  - Open for participation

[1]Clausen et al. Non-invasive foetal RhD genotyping to guide anti-D prophylaxis: an external quality assurance workshop. Bloodtransfusion DOI: 10.2450/2017.0329-16

Effect and consequence of the Danish Rh-program

- Clinical Effect of Antenatal Prophylaxis
  - Preliminary data show a decrease in number of immunizations
- Consequence of Noninvasive Fetal RhD Genotyping
  - > 97% of the women who carry RhD negative fetuses avoided unnecessary treatment.

Preliminary data from DK!



THANK YOU FOR YOUR ATTENTION!

My colleagues

- Morten H Dziegiel, MD PhD, Chief Physician[1,2]
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- Grethe Risum Krog, MBLSc, PhD Fellow[1]
- Leif Kofoed Nielsen, PhD[1,3]
- Ann Tabor, Professor[2,4]
- Angela Natalie Barrett, PhD[5]
- The staff from The Department of Clinical Immunology
- The Danish National Group for Noninvasive Fetal RhD Genotyping

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