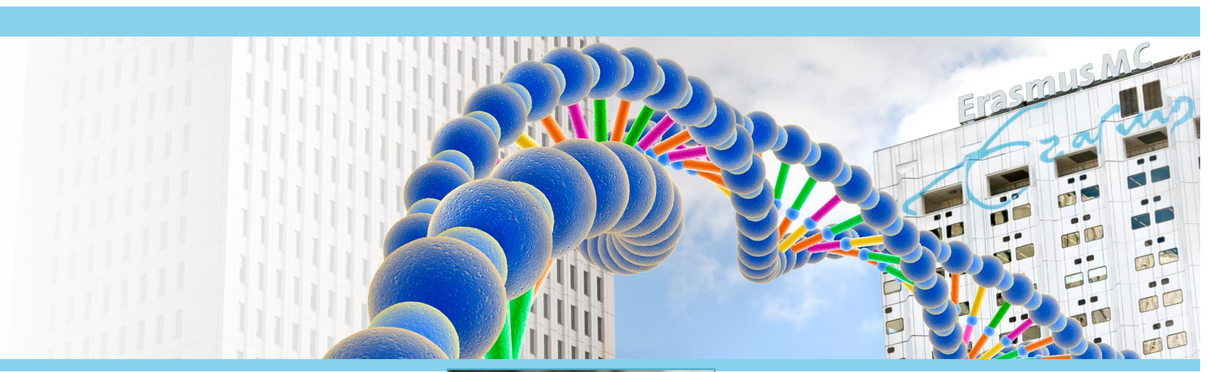
NIPT is more sensitive for detection of confined placental mosaicism (CPM) than chorionic villus sampling (CVS)



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Conclusion:

Little is known about how cytogenetic results of non-invasive prenatal testing (NIPT), chorionic villus sampling (CVS) and placenta relate to each other. We found evidence that NIPT is more sensitive for detection of confined placental mosaicism (CPM) than CVS, which may have clinical implications. We show that NIPT may detect CPM that is restricted to only a (small) part of the placenta, which may go undetected with CVS, that has a mitotic origin with no risk for fetal UPD, and probably also a small risk for placental malfunction as well as for fetal involvement of the trisomy. If (potential) CPM is detected with NIPT, the main goal will be to differentiate CPM that is associated with adverse pregnancy outcome from the ones without clinical consequences. Further research in this respect is needed.

Objective: In a high risk pregnant population (e.g. with abnormal combined test results) the association between confined placental mosaicism (CPM), especially CPM type 3, and adverse pregnancy outcome such as IUGR, IUVD, pregnancy complications and fetal congenital malformations has been shown. Nowadays, when a rare autosomal trisomy (RAT) is detected by NIPT, which is presumed to be present in the placenta (amniotic fluid normal), the risk for adverse pregnancy outcome is unknown. Little is known how results from NIPT compare to those from CVS and placenta. The question is whether potential CPM detected with NIPT in a general obstetric population is associated with an increased risk for an adverse pregnancy outcome. By doing cytogenetic follow-up investigations with chorionic villus sampling (CVS) and placental studies, we tried to get more insight into this association.

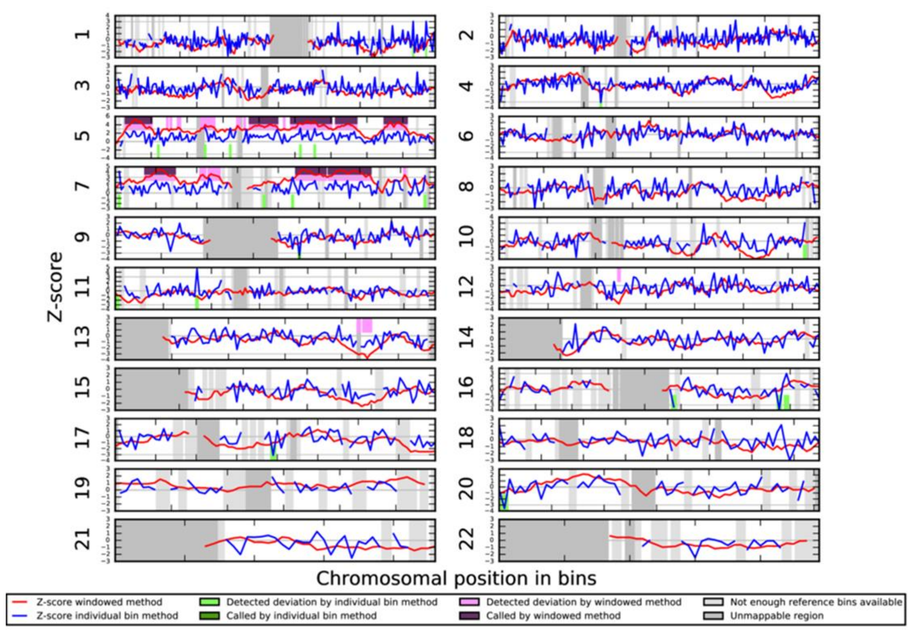
Results: In 20 cases of RAT, CVS was performed. In 12 cases the chromosome aberration was confirmed in CV and in 3 cases the mother showed to be mosaic. In the remaining 5 cases, CV were normal and placentas were collected. Four of 5 placentas revealed the RAT despite a normal CVS (table 1).

Table 1 cytogenetic investigations in CV and placenta and clinical outcome in 4 cases of RAT (one with double trisomy 5 and 7, and 3 cases of trisomy 8) as detected with NIPT

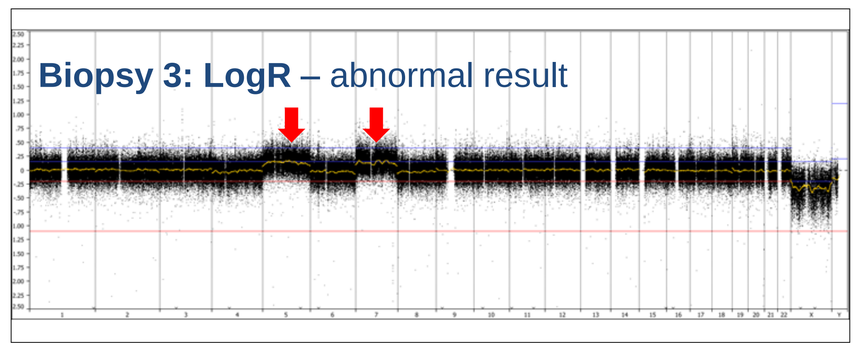
CV- chorionic villi, CTB- cytotrophoblast, MC- mesenchymal core, GA - Gestational age in weeks, FF- fetal fraction, CWAT- z-score of chromosome wide aneuploidy test in WISECONDOR, PPROM- Premature Preterm Rupture of Membranes, T-trisomy, N-normal

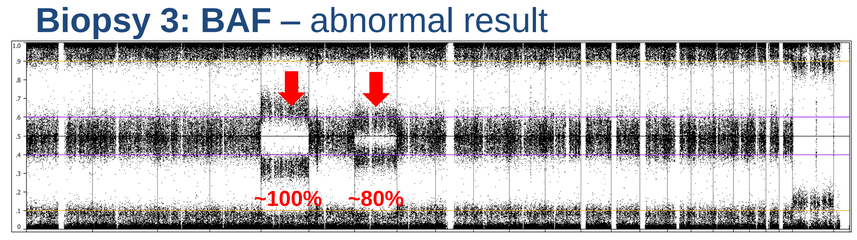
case	NIPT	GA	FF	z-score (CWAT)	Prenatal Cytogenetics (normal CTB and MC)			Postnatal cytogenetics			Clinical outcome
					GA	mg CV	mat blood	Placenta (4 CV biopsies)		Cord blood	
								CTB	MC		
1	T5 and T7	12	10.4% (DEFRAG)	chr5 13.5 chr7 11.6	14 3/7	8 mg	N	T5 and T7 in 1/4 biopsy (T5 100% and T7 80%)	N	N	N
2	T8	12	7.3% (DEFRAG)	7.4	14 1/7	15 mg	N	T8 in 1/4 biopsy (10%)	N	-	N
3	T8	17	7.5% (SeqFF)	9.5	19 1/7	20 mg	N	T8 in 3/4 biopsies (20%, 2x 100%)	T8 in 1/4 biopsy (10%)	-	Partus immatures (PPROM)
4	T8	11 5/7	17.5% (DEFRAG)	32.6	14 4/7	40 mg	N	T8 in 2/4 biopsies (2x100%)	N	N	N

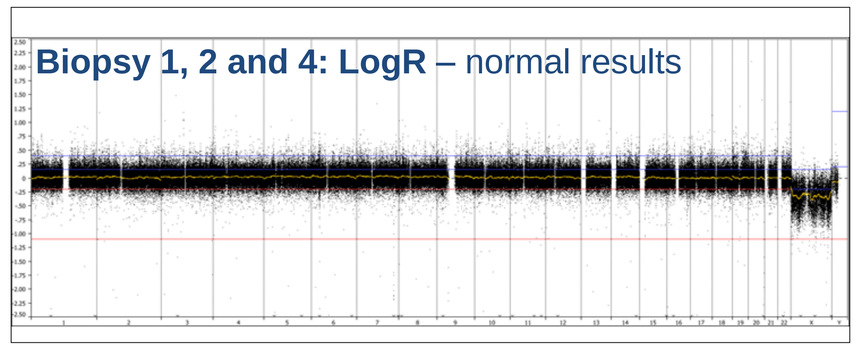
Prenatal results: NIPT-case 1



Postnatal placenta results: CTB of 4 biopsies - case 1







Material and methods: NIPT was performed as part of the Dutch Trident study. Genome-wide NIPT was performed using shallow massively parallel sequencing and WISECONDOR for analysis. For investigation of CV, both cytotrophoblast (CTB) and mesenchymal core (MC) were investigated with genomic SNP array (Illumina Infinium_CytoSNP_850K). In case of normal results in CV, the placenta was collected after delivery in order to investigate the presence of confined placental mosaicism (CPM). Placental cytogenetic studies involved the targeted analysis (only affected chromosome analysed!) of CTB and MC of four different quadrants with genomic SNP array and of cord blood in some cases.

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