Poster ID #171

Early detection of Human CytomegaloVirus (HCMV) infection in pregnant women: large-scale first trimester screening using data generated with whole-genome NIPT

Galuh Astuti[1], Janette C Rahamat-Langendoen[2], Annette Reuss[3], Christian Gilissen[1], Merryn Macville[4], Dominique FCM Smeets[1], Erik A Sistermans[5], Brigitte HW Faas[1]

[1]Department of Human Genetics, Radboudumc Nijmegen, [2]Department of Medical Microbiology, Radboudumc Nijmegen, [3]Department of Obstetrics and Gynecology, Radboudumc Nijmegen, [4]Department of Clinical Genetics, Maastricht University Medical Center+, Maastricht, [5]Department of Clinical Genetics, Amsterdam UMC, Amsterdam, The Netherlands

1. Objective

- Human CytoMegaloVirus (HCMV) infection is the most common congenital infection worldwide. It can be transmitted from mother to fetus, with a high risk on embryopathology when transmission occurs early in pregnancy.
- Recent studies have shown the possibility to strongly reduce maternal-fetal transmission after maternal primo-infection in the first trimester.
- In this study, we assessed the possibility to use data generated by whole genome noninvasive prenatal testing (NIPT) for the detection of HCMV-DNA in the maternal blood.

2. Materials and Methods

- Coded NIPT data (generated using paired-end whole genome sequencing) from ~130 000 pregnant women were recruited from MUMC+ (cohort 1) and AmsterdamUMC (cohort 2), The Netherlands, and aligned to the HCMV reference genome.
- To validate the NIPT-HCMV pipeline, routine diagnostic HCMV-PCR, IgG and IgM serology tests were performed on a selected group of 72 NIPT-HCMV-positive and 26 NIPT-HCMV-negative cases from cohort 1.
- HCMV-IgM- and –IgG-positivity, with or without positive PCR, was regarded as suggestive for a recent infection. Positive HCMV-IgG and negative IgM was interpreted as a previous infection.

3. Results

1. HCMV fragments were detected in ~1% of the NIPT samples, with fragment counts ranging from 1 to 180 fragments per positive sample.
2. Mean viral fragment length was 110 bp (Figure 1 in red), whereas the mean fragment length of the human DNA was 191 bp (Figure 1 in blue).
3. Based on routine HCMV diagnostics on 98 samples from cohort 1 (see Table):
   - NIPT-HCMV-positivity correlated well with HCMV-PCR positivity, especially in the samples with higher viral load (Figure 2),
   - NIPT-HCMV-negativity correlated well with non-suspected cases,
   - (Probable / possible) recent infections were detected in the NIPT-HCMV-positive samples.
4. Sub-dividing data from cohort 1 into data obtained before (n=40,087) and during the COVID-19 pandemic (n=22,901) showed a higher positivity rate during the pandemic (0.6% and 1.5%, respectively).

	IgG+/ IgM+		IgG-/ IgM-		IgG+/ IgM-		IgG-/ IgM+	
	PCR+	PCR-	PCR+	PCR-	PCR+	PCR-	PCR+	PCR-
NIPT +	23	7	1	4	5	30	2	
NIPT -		1		14		11		

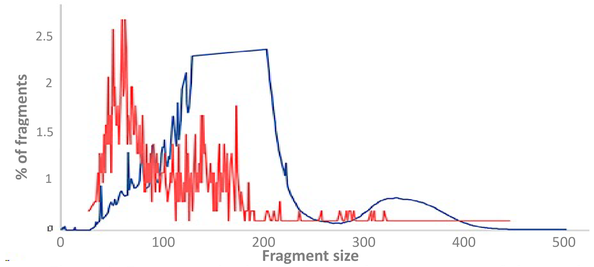

Figure 1. Fragment size in relation to the percentage of the total number of fragments with that size.

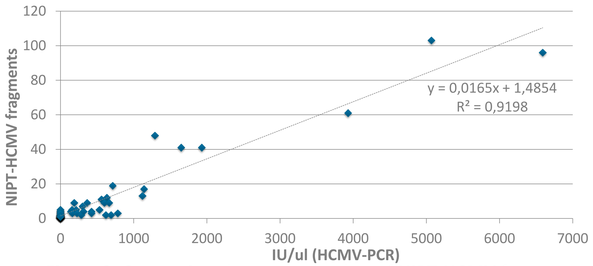

Figure 2. Comparison between number of NIPT-HCMV fragments and viral load, as calculated by HCMV-PCR.

4. Conclusions

Our first data suggest that HCMV-screening using data generated by NIPT could in future be a first step to enable identification of a primo-HCMV infection in the first trimester of pregnancy, as:

1. HCMV viral fragments could be detected in the blood of ~1% of the pregnant women.
2. In the subset of serologically tested samples, NIPT-HCMV-negativity correlated well with non-suspected cases based on routine HCMV diagnostics, whereas (probable / possible) recent infections were detected in the NIPT-HCMV-positive samples. There was only one sample, that tested negative with both NIPT and HCMV-PCR, but IgM- and IgG-positive, that was suggestive for a very recent infection based on serology.

Furthermore, the percentage of NIPT-HCMV-positive samples during the COVID-19 pandemic was higher than before the pandemic.

5. In future…

1. …IgG-avidity tests on all NIPT-HCMV-positive samples will be carried out to obtain more information on the exact timing and frequency of the infections,
2. …more insight will be needed in order to determine whether NIPT data can indeed be of use in screening for HCMV during pregnancy,
3. …a per month comparison before and during the pandemic is needed, as well as serology data, to differentiate between recent infections and re-activations, to understand the higher HCMV detection rate during the COVID-19 pandemic.

Radboudumc university medical center

Contact: Brigitte.faas@radboudumc.nl

This study was funded by the Prenatal Screening Foundation Nijmegen, The Netherlands

Human Genetics Nijmegen