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ORIGINAL RESEARCH

Maternal–fetal transfer and longitudinal trends of antibodies to *Chlamydia trachomatis* and *Mycoplasma genitalium* in early childhood

Nea Koskela[1] | Julia Butt[2] | Birgitta E. Michels[2] | Kari Syrjänen[3] | Seija Grenman[4] | Tim Waterboer[2] | Stina Syrjänen[5,6] | Karolina Louvanto[1,7]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

[2]German Cancer Research Center (DKFZ), Heidelberg, Germany

[3]SMW Consultants, Ltd, Kaarina, Finland

[4]Department of Obstetrics and Gynecology, Turku University Hospital, University of Turku, Turku, Finland

[5]Department of Oral Pathology, Institute of Dentistry, Faculty of Medicine, University of Turku, Turku, Finland

[6]Department of Pathology, Turku University Hospital, Turku, Finland

[7]Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere, Finland

Correspondence
Nea Koskela, Department of Obstetrics and Gynecology, Faculty of Medicine and Health Technology, Tampere University, Arvo Ylpön katu 34, 33520 Tampere, Finland.
Email: nea.koskela@tuni.fi

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Abstract

Introduction: Sexually transmitted infections caused by *Chlamydia trachomatis* and *Mycoplasma genitalium* can have significant implications during early childhood. This study aimed to assess maternal antibodies to *C. trachomatis* and *M. genitalium* in newborns, their vanishing, and offspring's own seroconversion to these pathogens during the first 3 years of life.

Material and Methods: Altogether, 309 mother-neonate pairs originally enrolled in the prospective Finnish Family HPV (FFHPV) cohort study at Turku University Hospital, Finland, were analyzed for serum IgG antibodies to plasmid protein gene 3 (pGP3) for *C. trachomatis* and *M. genitalium* protein of adhesion (MgPa N-term) and recombinant MgPa for *M. genitalium* using multiplex serology, by serial sampling during a 3-year follow-up.

Results: A significant correlation between maternal and neonate antibodies to both *C. trachomatis* and *M. genitalium* was evident up to 2 months after birth and to *C. trachomatis* also at 6 months ($p < 0.001$). During the first 3 years of life, three children seroconverted IgG antibodies to *C. trachomatis* and one to *M. genitalium*. At the last (36-month) follow-up visit, five (2.1%) children were seropositive for *C. trachomatis* and only one (0.4%) for *M. genitalium*.

Conclusions: Both *C. trachomatis* and *M. genitalium* IgG antibodies are transferred from the mother to her offspring during pregnancy; similarly, this is shown for nearly all maternal IgG antibodies. Seroconversion for both *C. trachomatis* and *M. genitalium* in early childhood was a rare event. Further studies are required to elucidate the significance of *C. trachomatis* and *M. genitalium* antibodies acquired in early life.

KEYWORDS
C. trachomatis, *M. genitalium*, maternal–fetal transfer, mother, newborn, serology

Abbreviations: *Ct*, *Chlamydia trachomatis*; IgG, immunoglobulin G; MFI, median fluorescence intensity; *Mg*, *Mycoplasma genitalium*; MgPa, *M. genitalium* protein of adhesion; pGp3, Plasmid Gene Protein 3; rMgPa, recombinant MgPa.

1 | INTRODUCTION

During pregnancy, the outcomes of sexually transmitted infections, for example, *Chlamydia trachomatis* (*Ct*) and *Mycoplasma genitalium* (*Mg*), might be potentially severe, affecting both the mother and her newborn. In women, these infections can lead to clinically significant conditions, including pelvic inflammatory disease, while in newborns, they have been associated with preterm birth and low birth weight. Additionally, some studies have reported a link to spontaneous abortion and increased perinatal mortality.[1,2] The two most common neonatal outcomes of *Ct* infection are pneumonia and conjunctivitis.[3] Neonatal outcomes of *Mg* are less well established due to a lack of studies.[4,5]

Worldwide, *Ct* is one of the most prevalent bacterial sexually transmitted infections and represents a major public health burden. The necessity of *Ct* screening for pregnant women has been debated for quite a while without reaching a definite consensus.[3] Global studies on *Mg* epidemiology are scanty, but according to a recently published comprehensive meta-analysis, *Mg* prevalence rates level off around 1.3% in developed countries and 3.9% in developing countries.[6] Among pregnant women, *Mg* prevalence was found to be 5.7% in a recent study,[7] and the mean estimates of *Ct* are around 11%.[3]

Quantification of different *Mg* and *Ct* serum antibodies in adults can provide means to evaluate past exposure or ongoing infection.[8,9] Previous studies have shown *Ct*-seropositivity to be associated with an increased risk of various fertility-related outcomes or pregnancy complications.[10,11] Plasmid protein gene 3 (PGP3-D-CT, also known as pGp3) stands out as the predominant antigen during *Ct* infection,[12,13] and the majority of infected individuals produce immunoglobulin G (IgG)-specific antibodies against pGp3.[14] pGp3 serology has demonstrated one of the highest sensitivities in detecting previously confirmed *Ct* infections as compared to other *Ct*-related antigens.[8,15] For *Mg*, the protein of adhesion (MgPa) serves as the principal adhesin protein and primary virulence factor, playing a crucial role in facilitating bacterial attachment to the host cells.[9,16] Previous *Mg* serology studies have assayed IgG antibodies targeting MgPa N-term and/or recombinant MgPa (rMgPa), which are parts of MgPa.[9,14]

Only IgG antibodies are transferred across the placenta to the offspring during pregnancy and are detectable during the first 6 months of life.[17] The maternal–fetal transfer of IgG depends on several factors, including maternal concentrations of total IgG and specific antibodies,[18] gestational age,[19] the integrity of the placental barrier, IgG subclass, and the nature of the antigen.[17] The fetus acquires the majority of these IgG antibodies during the last 4 weeks of pregnancy, and fetal IgG can exceed maternal IgG levels in normal pregnancies at full term.[20] The mother–child transmission of *Ct* has been reported before,[21] but the mother–neonate concordance in *Ct* or *Mg* serostatus has not been described so far.

This longitudinal study setting analyzed the mother-to-newborn transfer of *Ct* and *Mg* antibodies, the vanishing of the maternal antibodies, and factors associated with a child's seroconversion by serial testing of the offspring during the first 3 years of life.

Key message

Maternal IgG antibodies for *Chlamydia trachomatis* and *Mycoplasma genitalium* are transferred to the fetus during pregnancy, similar to other IgG antibodies. However, early-life seroconversion to these pathogens is rare.

2 | MATERIAL AND METHODS

2.1 | Subjects

The study is based on the prospective Finnish HPV Family Study (FFHPV) cohort study conducted at the Department of Obstetrics and Gynecology, Turku University Hospital, and the Institute of Dentistry, Faculty of Medicine, University of Turku, Finland since 1998. The study subjects include 329 mothers and 135 of their spouses, all enrolled (between 1998 and 2001) at the 36th week of pregnancy, as well as their 331 newborns, subsequently followed up for 3 years, as previously described in detail.[22] All study participants were of Caucasian descent and shared the same ethnic background.[23]

2.2 | Serology

Blood samples were collected at the baseline and subsequently at 12-, 24-, and 36-month follow-up visits from both spouses. Blood samples from the offspring were collected after birth and at 1-, 2-, 6-, 12-, 24-, and 36-month follow-ups. The samples were stored at −80°C until the serological analyses were conducted in 2022. The serological testing was performed at the German Cancer Research Center (DKFZ), Heidelberg, Germany, using the quantitative multiplex serology assay based on glutathione S-transferase (GST) capture ELISA combined with fluorescent-bead technology.[24] For *Ct*, the serum IgG antibodies to the immunodominant antigen pGp3 were measured.[13] For *Mg* serology, antibodies against two protein fragments (MgPa N-Term and rMgPa) of the primary virulence factor (MgPa) of this bacterium were analyzed.[16] The median fluorescence intensity (MFI) of at least 100 beads per antigen was measured. The seropositivity cut-off value for *Ct* (pGp3) was MFI >500, and that for *Mg* was MFI >1000 (both MgPa N-Term and rMgPa). Assay development and validation are described in detail earlier.[14]

2.3 | Statistical analyses

In total, 325 mothers and 312 of their offspring (two sets of twins) had at least one serum sample available and were included in the

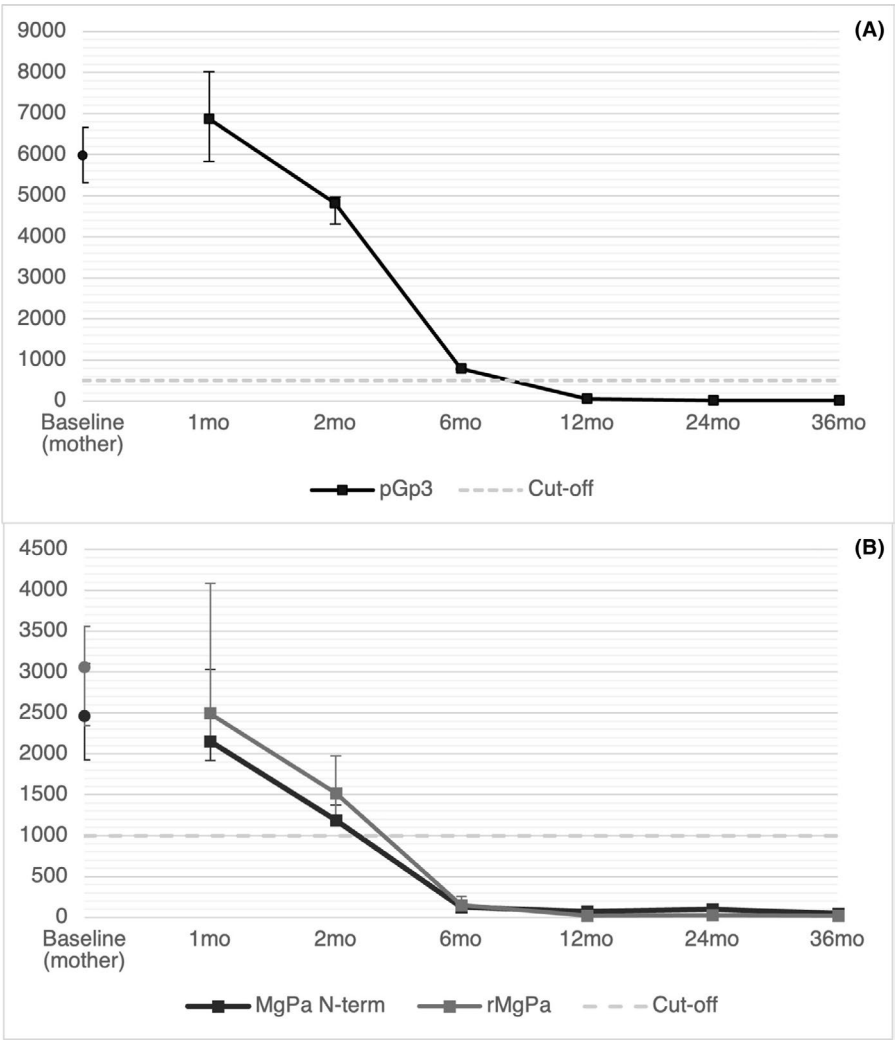

FIGURE 1 Median fluorescence intensity (95% CI) IgG-antibody titers to (A) *C. trachomatis* (*Ct*) antigen Plasmid Gene Protein 3 (pGp3) and (B) *M. genitalium* (*Mg*) antigens MgPa N-term and rMgPa of the children born to *Ct*/*Mg* seropositive mothers. MgPa *M. genitalium* protein of adhesion.

final analysis, with 309 complete mother–child pairs. Serostatus and antibody levels of the children were assayed at each follow-up visit, using the serostatus and antibody levels of their mothers at baseline as the reference. The seroconversion among the offspring was defined as an event where at least a two-fold increase in the antibody levels was seen at two consequent testings, and the levels remained above the cut-off level until the end of the follow-up.

Spearman's rank correlation coefficient (Spearman's rho) was used to evaluate the strength (and direction) of the bivariate correlation between maternal and newborn antibody levels at different time points. Correlations >0.6 were classified as strong, those between 0.4 and 0.6 as moderate, and those below 0.4 as weak. Two-sided *p*-values <0.05 were considered statistically significant. All statistical analyses were performed using STATA MP17.0 (Stata Corp., College Station, TX, USA).

3 | RESULTS

Of the 309 mother–child pairs, 97 (31.4%) mothers were seropositive to *Ct* and 48 (15.5%) to *Mg* at the baseline sample. The mothers' mean gestational age was 40.1 weeks, with 78.3% ($n=242$) being vaginal deliveries. The median antibody levels during the 36-month follow-up of the offspring born to mothers who were seropositive for *Ct* (A) and *Mg* (B) at enrollment underwent a deep decline between the 2- and 6-month visits for both pathogens (Figure 1). At the 6-month follow-up, the median of the offspring born to *Ct*-seropositive mothers remained seropositive, in contrast to *Mg*, where the median MFI titers fell below the cut-off values already at the 2-month follow-up visit. At the end of the 36-month follow-up, the antibody levels of both *Ct* and *Mg* in the offspring leveled significantly below the seropositivity cut-off values.

Maternal-to-neonate bivariate baseline antibody correlations were evident during the first 2 months for both *Ct* (range 0.94–0.97, $p<0.001$) and *Mg* (range 0.59–0.83, all significant at $p<0.001$ level) antibodies (Table 1). At 6 months, a significantly strong correlation persisted only for *Ct* (0.68, $p<0.001$). At 12 months, this correlation of *Ct* was weaker ($R<0.4$) but still significant ($p<0.001$).

The serostatus of the children to *Ct* antigen pGp3 and *Mg* antigens MgPa N-term and rMgPa during the 3-year follow-up is shown in Table 2. The proportion of *Ct* seropositive children peaked at the 2-month follow-up, 34.0% ($n=80$), whereas that of *Mg* (15.7% $n=36$) was evidenced already at the 1-month time point. During the follow-up, only three of the offspring showed seroconversion to *Ct*

at the 36-month follow-up. Only one child seroconverted to *Mg* at 12 months and remained seropositive until the end of the follow-up. As to these seroconverted offspring, all mothers tested seronegative at baseline, and all mothers remained seronegative during the whole 36-month follow-up. At 36 months, five of the offspring were seropositive for *Ct*, three being seroconverted and two who remained seropositive since birth, with extremely high MFI levels, ranging from 7343 to 10 986 and from 1344 to 5575, respectively.

TABLE 1 Bivariate correlations between the *C. trachomatis* (pGp3) and *M. genitalium* (MgPa N-term & rMgPa) antibody levels of the offspring (at follow-up visits) and those of their mothers at baseline. Substantial correlations ($R > 0.4$, $p < 0.001$) in bold.

Follow-up visits of the offspring	Mothers at baseline
1 month	
pGp3	**0.97**
MgPa N-term	**0.82**
rMgPa	**0.83**
2 month	
pGp3	**0.94**
MgPa N-term	**0.59**
rMgPa	**0.68**
6 month	
pGp3	**0.68**
MgPa N-term	0.16
rMgPa	0.10
12 months	
pGp3	0.31*
MgPa N-term	0.01
rMgPa	0.11
24 months	
pGp3	0.12
MgPa N-term	−0.05
rMgPa	0.09
36 months	
pGp3	0.05
MgPa N-term	−0.05
rMgPa	0.03

*$p < 0.001$, but ranking $R < 0.4$.

However, the children who seropersisted throughout the follow-up period have likely acquired their own antibodies on the way, as maternal antibodies are understood to wane within the first year of life.

Table 3 shows the serostatus of the parents of those children who tested *Ct* or *Mg* seropositive at their 36-month visit. There was only one offspring who seroconverted to *Mg* and stayed seropositive to the end of the follow-up. Their mother tested seronegative at three visits, and the father's data was missing. For *Ct*, the serostatus of the mother varied, as two were always negative, two were positive, and data from one mother was missing. There were only two families where the *Ct* results from the fathers were available, and both fathers were always seronegative.

4 | DISCUSSION

This study is the first to evaluate both the *Ct* and *Mg* antibodies among mother–neonate pairs, with a prospective follow-up of the offspring's serostatus during the first 3 years of life. These data confirmed a close correlation between maternal and neonate *Ct* and *Mg* IgG antibodies during the first 2 months after birth, and *Ct* antibodies also to 6 months. During the 3-year follow-up, three offspring seroconverted for *Ct*, and one did so for *Mg*. At the last 36-month follow-up visit, five (2.1%) children were seropositive for *Ct*, and one (0.4%) was seropositive for *Mg*.

As well known, newborns are provided with maternal antibodies acquired by placental transfer, and the neonates completely depend on those during the first months of their life. The nature and duration of this protection rely on the concentration of specific antibodies from the mother and the capacity of the mother to transfer these to the neonate.[17,18] By the time of birth, passively acquired fetal IgG exceeds maternal IgG concentrations, but these maternal antibodies directed to pathogen-specific antigens disappear during the first six to latest 12 months when the neonate's own immune system matures.[19] The present observations are in perfect alignment with this concept while confirming that both *Ct* and *Mg* antibody levels in the newborns exceeded the maternal antibody levels recorded at study entry (third trimester pregnant). During the fetal period, trans-placental IgG transfer starts already in the first trimester, but the majority of the IgG load is acquired by the fetus during the last 4 weeks of full-term pregnancy.[25] The children in this cohort were

TABLE 2 Seropositivity of the children to *C. trachomatis* (Ct) antigen pGp3 and *M. genitalium* (Mg) antigens MgPa N-term and rMgPa during the 3-year follow-up.

	1 month	2 months	6 months	12 months	24 months	36 months
Number at each visit	230	237	255	269	247	236
Seropositive to *Ct*, *n* (%)[a]	72 (31.3)	80 (33.8)	58 (22.7)	16 (5.9)	4 (1.6)	5 (2.1)
Seropositive to *Mg*, *n* (%)[b]	36 (15.7)	20 (8.4)	1 (0.4)	3 (1.1)	2 (0.8)	1 (0.4)
Ct seroconversion, *n* (%)	…	…	…	…	…	3 (1.3)
Mg seroconversion, *n* (%)	…	…	…	1 (0.4)	…	…

[a]Antigen cut-off for Ct seropositivity pGp3 MFI ≥500.

[b]Antigen cut-off for Mg seropositivity MgPa N-term and rMgPa MFI ≥1000.

TABLE 3 Serostatus of the parents to the offspring tested seropositive to *C. trachomatis* (Ct) ($n=5$) and *M. genitalium* (Mg) ($n=1$) at the 36-month follow-up.

Family	Delivery mode	Serostatus of the offspring during the follow-up	Serostatus of the parents[a] Baseline (Mo/Fa)[b]	12mo (Mo/Fa)	24mo (Mo/Fa)	36mo (Mo/Fa)
Ct						
I	*Vaginal*	*Always positive*	+/…	+/…	+/…	+/…
II	*Vaginal*	*Always positive*	+/…	+/…	+/…	+/…
III	*Vaginal*	*Seroconversion*	−/…	−/…	−/…	−/…
IV	*Vaginal*	*Seroconversion*	−/−	−/−	−/−	−/−
V	*Vaginal*	*Seroconversion*	…/−	…/−	…/−	…/…
Mg						
I	*Vaginal*	*Seroconversion*	−/…	−/…	−/…	…/…

[a]Positive at timepoint (+), negative (−), no data available (…).

[b]Mo, mother; Fa, father.

all born full term, with a mean of 40.1 gestational weeks, which also explains the high antibody levels in the offspring born to seropositive mothers.

Given the known half-life of IgG molecules, maternal antibodies in neonates are known to wane in approximately 6–12 months.[26] The kinetics of maternal antibody decay are correlated to the levels of maternal antibodies present at birth, and higher titers of maternal antibodies are known to persist for a longer time.[27] In the present offspring cohort, this 6-month (average) IgG vanishing pattern held perfectly for maternal *Ct* antibodies, whereas *Mg* antibodies fell below the cut-off level before the 6-month follow-up point. This subject has not been specifically studied in the context of *Ct* or *Mg*, and multiple explanations for these differences in the persistence of maternal *Ct* and *Mg* antibodies are likely to exist. These might include (i) the immunological characteristics of the pathogens and antigens, (ii) the efficiency of placental IgG transfer (e.g., via FcRn), and (iii) possibly different maternal exposure to these pathogens. In our study, seropositive mothers' baseline mean antibody levels for *Ct* (pGp3 MFI = 5834) were significantly higher than for *Mg* (MgPa N-term MFI = 3087, rMgPa MFI = 3301). These mothers' high *Ct* antibody levels also coincided with the higher antibody levels in their offspring; at 1 month, the mean MFIs in the children were 7180.676 (pGp3), 2680.083 (MgPa N-term), and 3214.222 (rMgPa).

The most common clinical outcomes of *Ct* infection among neonates are pneumonia and conjunctivitis,[3] ranging between 0% and 17% and 8% and 44% of the cases,[28] respectively. Compared to vaginal delivery, Cesarean section has been shown to reduce the *Ct* transmission rates even after the rupture of the membranes, but not completely prevent the transmission of *Ct* infection among newborns whose mothers were *Ct* infected.[29] *Ct* IgM antibodies have been linked to systemic chlamydial infection and could be used to diagnose chlamydial pneumonia in infants.[21] *Ct* IgG antibodies are frequently detected in sera from mothers with stillbirth (suggesting past infection), while mothers with preterm delivery often have serum IgM antibodies (suggesting a newly acquired infection).[30] In our cohort, the majority of the children were born vaginally (78.3%), leaving little room for speculation about the effect of the delivery mode.

We further conducted a detailed examination of the characteristics of the six children who either seroconverted *Ct/Mg* or exhibited prolonged seropersistence (Table 3). While *Ct* infection can indicate sexual abuse in children, perinatal transmission from infected mothers is common, posing up to a 50%–75% risk of infection in newborns.[31] These perinatally acquired infections can persist for 2–3 years in areas such as the nasopharynx, urogenital tract, and rectum. An earlier study showed a progressive increase in *Ct* seropositivity with age, ranging from 5% for 1- to 2-year-olds, 25% for 3- to 6-year-olds, and 43% in 7- to 15-year-olds.[32] Furthermore, seropositivity rates were not related to sex or race, indicating that *Ct* infection is relatively common among children. *Ct* transmission might occur via infected siblings or through respiratory tract infections.[31] Also, there might be cross-reactivity between antigens of *C. pneumonia* and *Ct*, resulting in false-positive serology. Nevertheless, the origin of *Ct* or *Mg* infection leading to IgG antibody response in children in our study remains unclear. Future follow-up studies are needed to assess *Ct* and *Mg* antibodies in children and serology's significance during the first years of life.

The correlation of *Mg* IgG-antibodies in mother-neonate pairs has not been previously analyzed. Similarly, studies on vertical transmission of *Mg* infection are scant.[33] A small study on pregnant women from Israel reported a 2.3% pathogen carriage rate for *Mg* ($n=5$), and only one offspring was born with *Mg* infection.[34] To date, the most acknowledged and commonly reported pregnancy-related outcomes associated with *Mg* infection are low birth weight[35,36] and preterm birth.[1] One study also examined the association between *Mg* serology and ectopic pregnancy but did not find any significant correlation.[4] Regarding mycoplasma-associated health problems in newborns, there is inconsistent evidence suggesting that *Mycoplasma hominins* may cause neonatal conjunctivitis.[33] So far, however, the involvement of *Mg* in such conditions has not been confirmed, and

Mg is not believed to have any role in respiratory tract diseases in newborns, unlike certain other mycoplasma and *Ct*.[5] Our preliminary data confirm that at least *Mg* antibodies are transferred from the mother to the child, but additional studies are needed to assess the significance of *Mg* infections and their seropositivity in infants.

Ct is an easily curable infection, and antenatal screening programs that identify and treat infected mothers could prevent many pregnancy and neonatal complications. In the United States, the routine implementation of *Ct* screening and treatment lowered the pediatric seroprevalence and neonatal conjunctivitis.[37] Also, studies from Australia and the Netherlands demonstrated *Ct* screening to be cost-effective in preventing morbidity associated with chlamydial infections, particularly among younger pregnant women.[38,39] In Finland, pregnant women are not systematically screened for *Ct*. Only women who ask for the test or have symptoms related to the risk of preterm birth are tested because *Ct* has been associated with various pregnancy complications.[2] In the Finnish Family HVP Study (FFHPV) cohort of pregnant women, the baseline *Ct* or *Mg* infection status was not controlled. However, 10.7% ($n=33$) of these women reported a history of having a *Ct* infection diagnosed in the past. Among the offspring of these mothers, there were no significant differences either in the MFI levels or in the duration of the antibodies as compared to the overall means. Persistent chlamydial infections acquired neonatally have been associated with significant long-term consequences in both the eyes and lungs, although these are rare.[40] Therefore, timely diagnosis and treatment are crucial for both the child and the mother to avoid potential long-term risks.

The strength of our study is the longitudinal setting with serial sampling of over 300 mother –neonate pairs for serological testing of *Ct* and *Mg* to determine antibody levels during the 3-year follow-up. In addition, the serological assay used has been carefully validated,[14] providing accurate MFI levels of the tested antibodies among the cohort participants. Our limitation is the missing systematic confirmation of the clinical *Ct* or *Mg* infections of both parents during the follow-up. NAAT testing of the children exhibiting prolonged seropersistence, along with their mothers, would have been highly valuable in determining whether seropersistence resulted from a vertically transmitted infection at birth.

5 | CONCLUSION

To conclude, both *Mg* and *Ct* antibodies are transferred from the mother to the newborn. As expected based on the known half-life of IgG, the *Ct* antibodies persisted for up to 6 months or even to 12 months, whereas *Mg* antibodies in the majority of infants persisted for a shorter time, less than 6 months. However, few infants acquired their own antibodies and/or remained even seropositive throughout the entire follow-up. The reasons for the divergent behavior of maternal *Ct* and *Mg* antibodies in these infants remain unclear, as well as the offspring's seroconversion to these microbes. Additional studies are needed to elucidate the possible clinical significance of these early-life serological responses to *Ct* and *Mg* among infants.

AUTHOR CONTRIBUTIONS

Birgitta E. Michels: Methodology, software, formal analysis, investigation, data curation, writing—review and editing. **Julia Butt:** Methodology, software, formal analysis, investigation, data curation, writing—review and editing. **Kari Syrjänen:** Software, validation, formal analysis, investigation, data curation, writing—review and editing. **Karolina Louvanto:** Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—review and editing, visualization, supervision, project administration, funding acquisition. **Nea Koskela:** Formal analysis, investigation, writing—original draft preparation, review and editing, visualization. **Seija Grenman:** Conceptualization, methodology, investigation, data curation, writing—review and editing. **Stina Syrjänen:** Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—review and editing, visualization, supervision, project administration, funding acquisition. **Tim Waterboer:** Methodology, software, validation, formal analysis, investigation, data curation, writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The Research Ethics Committee of Turku University Hospital has approved this study design and its amendments (#3/1998, March 31, 1998; #2/2006, February 21, 2006; and 45/1801/2018, August 7, 2018). Informed written consent was obtained from all participants.

ORCID

Nea Koskela https://orcid.org/0009-0002-0337-7420

Karolina Louvanto https://orcid.org/0000-0002-1172-363X

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