

# The Impact of Maternal Infection with Cytomegalovirus, Parvovirus B19, and Toxoplasma gondii on Fetal Thymus Size

**Christina Marie Becker**

University Hospital Münster

**Mareike Möllers**

University Hospital Münster

**Moritz Danzer**

University of Münster

**Anna-Lena Kuper**

University Hospital Münster

**Kathrin Oelmeier**

University Hospital Münster

**Ralf Schmitz**

Florence-Nightingale-Hospital

**Daniela Willy**

`daniela.willy@ukmuenster.de`

University Hospital Münster

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## Research Article

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# Abstract

## Purpose

To assess the effect of maternal infection with cytomegalovirus (CMV), parvovirus B19 (B19V) and *Toxoplasma gondii* (*T. gondii*) during pregnancy on fetal thymus size.

## Methods

We retrospectively analysed fetal thymus size in 146 pregnancies of infected mothers (study group) between 14th and 37th weeks of gestation and compared these to a group of 303 healthy pregnancies (controls). To determine fetal thymus size, the thymic-thoracic ratio (TTR) was calculated by dividing the anteroposterior thymic diameter by the intrathoracic mediastinal diameter in the three vessel and trachea (3VT) view in fetal echocardiography. Additionally, the study group was subdivided according to maternal infection pathogen, respectively CMV, B19V and *T. gondii*, and according to fetal infection status, and a multiple linear regression was performed.

## Results

Fetal thymus size was found to be significantly larger in case of maternal infection with CMV, B19V and *T. gondii* during pregnancy in comparison to the controls. The mean TTR in the study group was 0.388 and 0.360 in the control group ( $p < 0.001$ ). The regression showed that maternal infections with all three pathogens were associated with an increase in TTR.

## Conclusion

Maternal CMV, B19V and *T. gondii* infections during pregnancy were associated with an increased fetal thymus size. Although the underlying mechanisms and implications on the developing immune system require further study, these findings may help identify pregnancies at risk and assess fetal infection status in the future.

## What does this study add to the clinical work?

We found a significantly increased fetal thymus size in pregnancies complicated by maternal CMV, B19V and *T. gondii* infection. Pending future validations, the measurement of TTR may contribute to the early identification of maternal infection and to the assessment of fetal infection status, potentially helping to reduce infection-related fetal damage.

## Introduction

Intrauterine infections remain an important cause of stillbirth and severe fetal damage, with cytomegalovirus (CMV), parvovirus B19 (B19V) and *Toxoplasma gondii* (*T. gondii*) among the most relevant causative pathogens [1,2]. All three pathogens can be transmitted vertically across the placenta during pregnancy, leading to fetal infection. Adverse outcomes caused by these infections include for example hearing loss, visual impairment, neurological alterations and severe anemia of the fetus [1–3]. With a birth prevalence of 0.64% [4], congenital infection with CMV (cCMV) is the most common intrauterine infection and a major cause of non-genetic hearing loss [5,6]. Further, cCMV can lead to several clinical findings such as growth restriction, ventriculomegaly, hydrocephaly and hepatosplenomegaly [7,8]. Although intrauterine infection with B19V is less frequent, an increase in B19V-infections among pregnant women was observed at the end of 2023 and beginning of 2024 [9]. According to Enders et al. congenital B19V infection (cB19V) may lead to fetal death in 11% if infection occurs during the first 20 weeks of gestation [10]. B19V infects erythrocyte-progenitor cells which can result in severe fetal anemia, at the same time non-immune hydrops fetalis, myocarditis and spontaneous abortion are observed [11,12]. Even though there could be many negative consequences if intrauterine infection with B19V occurs, it does not cause congenital malformations, as do CMV and *T. gondii*. In Germany, the seroconversion rate for *T. gondii* is estimated to be 1.3% per year for women of childbearing age [13]. Ultrasonographic findings indicative of congenital toxoplasmosis (cT) include hydrocephaly, intracerebral calcifications, ventriculomegaly, ascites as well as hepatosplenomegaly. A common late-onset complication of cT is chorioretinitis, which can subsequently result in severe visual impairment [1]. Since systematic screening for these three pathogens is not part of standard obstetrical care in Germany, and maternal CMV, B19V and *T. gondii* infections are frequently asymptomatic or present with unspecific symptoms, prenatal ultrasound is crucial in their detection. Early recognition of maternal and fetal infection is important, as it allows the use of available therapeutic and preventive measures that may improve fetal outcome. These include maternal treatment for CMV and *T. gondii* infection and, when indicated, intrauterine transfusion in cases of cB19V infection with subsequent fetal anemia [1,14–16].

The thymus is a primary lymphoid organ that plays a key role in the development of the adaptive immune system. The organogenesis of the thymus starts as early as in week 6 during pregnancy [17] and thereby highly influences the physiological development and function of the adaptive immune system. Since the thymus develops this early in pregnancy, several prenatal studies have focused on it [18]. The thymic-thoracic ratio (TTR) has been well established as an easy measurement of the thymus size in the three vessel and trachea (3VT) view, a standard plane in fetal echocardiography. It is calculated by dividing the anteroposterior diameter of the thymus by the intrathoracic mediastinal diameter (Figure 1) [19]. This size was shown to be independent from gestational age and maternal BMI [19–21]. Various pathological conditions during pregnancy have been associated with alterations in TTR, highlighting its clinical value [20,22,23]. For maternal infections and inflammatory conditions, previous studies have shown that maternal COVID-19 infection as well as maternal familial Mediterranean fever are associated with a smaller fetal thymus size, whereas HIV-positive mothers appear to have fetuses with increased thymus size [22–24]. Further studies have demonstrated the presence of CMV and *T. gondii* in thymic

tissue [25,26] and suggested that infection with these pathogens may result in immunological alterations [27,28]. The role of B19V in myasthenia gravis-related thymic hyperplasia has been discussed and remains controversial [29,30]. Even though CMV, B19V and *T. gondii* are relevant prenatal infections, the impact on the fetal thymus is unclear. Based on the above-mentioned findings, we hypothesized that maternal CMV, B19V and *T. gondii* infection might have an impact on fetal thymus size. The aim of this study was therefore to investigate on this impact while contrasting whether maternal infection resulted in congenital infection and if fetal infection itself affects the thymus size.

## Methods

In a retrospective analysis, data were extracted on all women with CMV, B19V, or *T. gondii* infection during pregnancy who received prenatal ultrasound examination between the 1st of January 2010 and the 31st of March 2025 at the Department of Obstetrics and Gynecology of the University Hospital Münster. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Board (Reference Number: 2025-329-f-S). The prenatal ultrasound screening including echocardiography was performed between the 14th and 37th week of gestation by experts in prenatal diagnostics. Ultrasound images and data were acquired from the Viewpoint Database (ViewPoint 6, ViewPoint 5) and ORBIS (Electronic Health Record system). We included women with confirmed infection occurring during the first, second, or third trimester. Consequently, women with infection reactivation or primary infection at a non-susceptible time were excluded. As described by Enders and Kagan, we considered seroconversion (newly detected IgG), concomitant IgM and IgG positivity, low IgG avidity (indicating a recent infection in the case of CMV) and an increase in IgG titers (in case of *T. gondii*) indicative of maternal infection [31]. Detection of the pathogen in amniotic fluid provided evidence of cCMV and cT [31]. Fetal anemia was assessed by Doppler examination of the peak velocity of the middle cerebral artery [32] and was considered confirmatory of cB19V once maternal infection was confirmed and other causes of fetal anemia excluded. We excluded all cases in which an ultrasound image of the fetal thymus in the 3VT view was either missing, of insufficient image quality or acquired before the onset of maternal infection. Further exclusion criteria were multiple pregnancies, fetal chromosomal aberrations, and other major congenital anomalies including heart defects and/or known abnormalities in thymus size (e.g. DiGeorge syndrome). Based on the pathogens, we built subgroups for CMV, B19V and *T. gondii* in the study group. Additionally, we subdivided the study group into three other groups regarding the fetal outcome: healthy infants, intrauterine infected infants and those with unknown outcome. The control group includes randomly selected singleton pregnancies without major complications, all of which were carried to term. The same exclusion criteria were applied.

## Measuring method

The fetal thymus size was measured in a standardized transverse plane in fetal echocardiography: the 3VT view (Fig. 1). In this plane, the thymus is visualized between the sternum and the three great vessels (pulmonary artery, aorta, and superior vena cava) in the upper mediastinum [19]. As described by Chaoui

et al., fetal thymus size was assessed by measuring the TTR. This ratio is calculated by dividing the anteroposterior thymic diameter by the intrathoracic mediastinal diameter [19].

$$TTR = \frac{\text{Anteroposterior thymic diameter}}{\text{Intrathoracic mediastinal diameter}}$$

To measure the mediastinal diameter, we drew a line with the ultrasound cursor from the posterior edge of the sternum to the anterior border of the vertebral body, crossing the aorta. For the thymic diameter, the measurement reached from the same spot at the posterior border of the sternum to the anterior border of the aorta, aligned to the drawn line of the mediastinal diameter. These measurements were conducted by two observers and reviewed by two independent examiners.

## Statistical methods

For statistical analysis, IBM SPSS Statistics, version 30.0 for macOS (IBM Corporation, Armonk, NY, USA) was used. Descriptive analyses were conducted for the overall study population and all predefined subgroups with respect to maternal baseline characteristics, fetal thymus, and outcome parameters. Normally distributed variables are reported as mean  $\pm$  standard deviation (SD) and were compared using t tests for two group comparisons or analysis of variance (ANOVA) for comparisons involving more than two groups. Non-normally distributed variables are reported as median and for group comparisons, Mann-Whitney-U-Test (for two groups) or Kruskal-Wallis-Test (for more than two groups) were applied. To further explore differences in TTR between groups, pairwise comparisons were performed between the CMV, B19V, *T. gondii* and the control group using the Games-Howell post hoc test. Additionally, TTR was compared between the subgroups of healthy infants and congenitally infected infants using a t test. Finally, a multiple linear regression was calculated to estimate the association between the TTR and maternal infection with CMV, B19V and *T. gondii* while additionally adjusting for intrauterine infection. Pregnancies with incomplete data were excluded from the analysis, if applicable. All results of statistical analysis were intended to be exploratory, not confirmatory. Accordingly, no correction for multiple testing was made. P-values and confidence intervals were two-sided and considered statistically significant when p-values  $\leq$  0.05.

## Results

We analysed 449 cases of which 146 cases were included in the study group and 303 cases comprised the control group. Table 1a presents baseline and outcome characteristics that were compared between the study group and the controls. Maternal age was lower in the study group than in the controls (30.58  $\pm$  4.82 vs. 32.79  $\pm$  4.69,  $p < 0.001$ ), whereas the gestational age at the ultrasound screening was higher in the study group (21.43 (14.57-37) vs. 20.71 (19–34),  $p = 0.049$ ). All other baseline and outcome characteristics did not differ significantly between the two groups, neither did the gender distribution according to available records (study group: 53.7% female, 46.3% male; controls: 47.2% female, 52.8% male;  $p = 0.32$ ).

In the study group, the TTR was significantly higher than in the controls ( $0.388 \pm 0.072$  vs.  $0.360 \pm 0.055$ ,  $p < 0.001$ , Table 1b). The distribution of the TTR in both groups is visualized in Fig. 2. Table 2 shows the composition of the study population according to maternal infection pathogen and fetal outcome. Figure 3 illustrates the distribution of the TTR in those groups. In the CMV group, the TTR had a mean of  $0.389 (\pm 0.074)$ , in the B19V group of  $0.384 (\pm 0.069)$  and in the *T. gondii* group, it was the highest at  $0.391 (\pm 0.071)$ . A statistically significant difference was observed between the CMV group and the controls with a mean difference at  $-0.029$  ( $p = 0.008$ ). When comparing the TTR by fetal outcome (healthy infants,  $n = 51$ ; intrauterine infected infants,  $n = 33$ ), there was no significant difference found between the group of healthy infants and those with intrauterine infection ( $p = 0.092$ ). The multiple linear regression model, including CMV, B19V, *T. gondii* and adjusting for the factor of intrauterine infection, was statistically significant ( $F(4,382)=6.078$ ,  $p < 0.001$ ). The  $R^2$  for this model was  $0.06$  (adjusted  $R^2 = 0.05$ ), indicating a small effect size according to Cohen (1988) [33]. Maternal infection with CMV, B19V and *T. gondii* was associated with an increase in TTR, with positive regression coefficients for all three pathogens (respectively,  $B = 0.044$ ,  $B = 0.049$ ,  $B = 0.040$ ; Table 3). These associations were statistically significant ( $p$ -values  $< 0.05$ ). In contrast, intrauterine infection was associated with a decrease in TTR, as indicated by a negative regression coefficient ( $B=-0.032$ ), but did not reach statistical significance ( $p = 0.051$ ). Within the overall study population, intrauterine infection resulted in nine cases in intrauterine fetal death, all of them associated with cB19V. In the B19V group, we compared the TTR between those nine cases and the pregnancies carried to term. TTR was significantly lower in pregnancies that were terminated by IUFD than in those that were carried to term, respectively  $0.330 \pm 0.073$  vs  $0.422 \pm 0.052$  ( $p < 0.001$ , Fig. 4).

Table 1

(a) Baseline and outcome characteristics and (b) fetal thymus measurements of the study group and the control group

| a | Parameter                 | Study group        | n   | Control group       | n   | P-values |
|---|---------------------------|--------------------|-----|---------------------|-----|----------|
|   | Age (years)               | 30.58 ± 4.82       | 146 | 32.79 ± 4.69        | 303 | < 0.001  |
|   | BMI (kg/m <sup>2</sup> )  | 23.12 (16.38–43.6) | 139 | 22.49 (16.23–57.63) | 297 | 0.136    |
|   | GA at screening (weeks)   | 21.43 (14.57–37)   | 146 | 20.71 (19–34)       | 303 | 0.049    |
|   | GA at birth (weeks)       | 39.14 (16.29–42)   | 86  | 39.14 (23.71–42.14) | 303 | 0.959    |
|   | Birth weight (g)          | 3377.50 (60–4740)  | 82  | 3235 (430–4800)     | 303 | 0.323    |
|   | Birth weight percentile   | 53.18 ± 27.52      | 80  | 50.41 ± 25.54       | 303 | 0.397    |
|   | Apgar score 5 min         | 10 (4–10)          | 73  | 10 (0–10)           | 302 | 0.969    |
|   | Apgar score 10 min        | 10 (0–10)          | 72  | 10 (0–10)           | 300 | 0.213    |
|   | pH umbilical artery       | 7.27 ± 0.077       | 69  | 7.28 ± 0.076        | 295 | 0.356    |
| b | Mediastinal diameter (mm) | 24 (12.3–52.1)     | 146 | 22.4 (14.8–41.5)    | 303 | 0.053    |
|   | Thymic diameter (mm)      | 9.4 (2.7–24.7)     | 146 | 8.1 (3.78–17.4)     | 303 | < 0.001  |
|   | TTR                       | 0.388 ± 0.072      | 146 | 0.360 ± 0.055       | 303 | < 0.001  |

Data listed as mean ± standard deviation or median (minimum, maximum). Univariate P-values are from t-tests (normally distributed) or Mann-Whitney U-tests (non-normally distributed) for independent groups. Valid values for the variables vary due to missing values. BMI = Body mass index; GA = gestational age; TTR = thymic-thoracic ratio.

Table 2  
Study subgroups by pathogens and fetal outcome

| Subgroups by fetal outcome       | CMV (n = 81) | B19V (n = 40) | <i>T. gondii</i> (n = 25) | Total (n = 146) |
|----------------------------------|--------------|---------------|---------------------------|-----------------|
| Healthy infants                  | 27 (33.3%)   | 9 (22.5%)     | 15 (60%)                  | 51 (34.9%)      |
| Intrauterine infected infants    | 10 (12.3%)   | 23 (57.5%)    | 0 (0%)                    | 33 (22.6%)      |
| Pregnancies with unknown outcome | 44 (54.3%)   | 8 (20%)       | 10 (40%)                  | 62 (42.5%)      |

CMV=Cytomegalovirus, B19V=Parvovirus B19, *T. gondii* =*Toxoplasma gondii*.

Table 3  
Regression coefficients for predicting the thymic-thoracic ratio

| Variable                      | B      | Standard Error | P-values | 95% CI for B |
|-------------------------------|--------|----------------|----------|--------------|
| Constant                      | 0.360  | 0.003          | < 0.001  | 0.353,0.367  |
| Cytomegalovirus               | 0.044  | 0.011          | < 0.001  | 0.022,0.066  |
| Parvovirus B19                | 0.049  | 0.016          | 0.003    | 0.017,0.08   |
| <i>Toxoplasma gondii</i>      | 0.040  | 0.016          | 0.011    | 0.009,0.071  |
| Intrauterine infected infants | -0.032 | 0.016          | 0.051    | -0.063,0     |

Reference categories: control group, healthy infants. Pregnancies with unknown outcome were excluded from this analysis.

## Discussion

In our study, we found that maternal infection with CMV, B19V and *T. gondii* is associated with an increase in fetal thymus size. This suggests that maternal infection with these pathogens may have an impact on the fetal thymus and thus on the developing immune system. To our knowledge, this is the first study to analyse the association between maternal infection with one of these three frequent pathogens and fetal thymus development.

In the subgroup analysis, a significant difference regarding TTR was found between CMV and the control group, but not between B19V or *T. gondii* and controls, respectively. However, after adjusting for intrauterine infection in the multiple linear regression, all three maternal infections showed a significant difference compared to the controls. To account for multiple comparisons and ensure comparability with post hoc testing, a Bonferroni correction was applied. All comparisons remained statistically significant ( $p < 0.05$ ) even after correction ( $p < 0.0125$ ). Accordingly, multivariable analysis demonstrated that all three pathogens were significantly associated with an increase in TTR.

Previous studies have already reported associations between maternal diseases and increased fetal thymus size, including HIV-infection, rheumatic diseases in first-trimester screening, and Hashimoto thyroiditis [22, 34, 35]. In HIV-exposed but uninfected infants, altered cytokine levels in cord blood [36] and transplacental transfer of viral soluble factors, in absence of active viral RNA [37], have been proposed to impact the fetal thymopoiesis and may contribute to thymic enlargement [22]. Histologically, two forms of thymic hyperplasia are known: true thymic hyperplasia, including rebound hyperplasia following stressors such as pneumonia, chemotherapy or corticosteroid therapy and lymphoid thymic hyperplasia typically observed in autoimmune diseases such as Myasthenia gravis (MG) [38]. The relationship between B19V and MG remains controversial. However, Gong et al. detected B19V DNA in 28 out of 68 samples of thymic hyperplasia [29]. For CMV, B19V and *T. gondii*, the immunological effects of vertical exposure, especially regarding the development of the thymus, remain uncertain. Still, these observations raise the possibility of fetal immune activation in response to maternal infection, potentially presenting as an increased fetal thymus size.

Conversely, maternal conditions such as familial Mediterranean fever, COVID-19-infection and asthma attacks during pregnancy have been associated with a decrease in fetal thymus size [23, 24, 39]. All of these conditions come along with maternal clinical or subclinical inflammation. It is known that fetal systemic inflammation, an early activated hypothalamic-pituitary-adrenal axis and thereby increased levels of corticosteroids can lead to a smaller fetal thymus [40, 41]. The role of maternal inflammation in the context of mostly asymptomatic maternal infection with CMV, B19V and *T. gondii* and its subsequent potential effect on fetal thymus development remain unclear.

We did not observe a significant association between confirmed fetal infection and TTR in either the group comparisons or the regression analysis. The regression indicated that the occurrence of intrauterine infection reduces the TTR but shortly did not reach statistical significance ( $p = 0.051$ ). It is commonly understood that active infection has harmful effects on the thymus and can result in thymic involution [42]. Similarly, Jeppesen et al. reported a smaller thymus size in hospitalized preterm neonates with neonatal infection, defined by positive blood culture or other clinical, laboratory and radiological indicators [43]. Furthermore, the thymus was found to be smaller in fetuses and neonates of mothers with chorioamnionitis, as well as in newborns with early-onset sepsis [44, 45]. This highlights the relationship between thymic involution and infectious and inflammatory conditions.

Previous studies have shown that smaller thymus size in infants is associated with increased mortality [46, 47]. In our study, IUFD rates were notably high in case of B19V infection and a significantly smaller fetal thymus size was observed in affected fetuses before the IUFD occurred. This finding might suggest an association between fetal thymus size and survival but the relationship between thymus size, infection severity, fetal anemia and survival remains unclear and needs to be further investigated.

Limitations of our study include heterogeneity in the timing of maternal infection, as susceptibility to fetal infection varies over the course of pregnancy, and variability in the interval between maternal infection and screening. Nevertheless, we analysed a high number of patients while applying stringent

inclusion criteria which ensured reliable identification of acute maternal infection and overall, a very high quality of the presented data. The retrospective and single-center design constitute limitations and may introduce bias, as well as potential measurement errors due to slight deviations from the optimal 3VT view for TTR measurement. Further, subgroup analysis allowed for differentiated results regarding pathogens and fetal outcome. Finally, TTR represents a simple and cost-efficient parameter, as the 3VT view is part of fetal standard echocardiography and shows a good intra- and interobserver reliability [48].

In conclusion, this study indicates that maternal infection with CMV, B19V and *T. gondii* is associated with an increased fetal thymus size. To better understand thymic responses to maternal and fetal infection in terms of growth and involution, as well as their consequences for the infantile immune system, further prospective studies are needed. Clinically, TTR may represent in the future a promising additional screening parameter to help evaluate maternal infection and pregnancies at risk.

## Declarations

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**Ethics Approval:** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee Westfalen-Lippe (Reference Number:2025-329-f-S).

**Consent:** Due to the retrospective design, obtaining the patient's informed consent was not required.

**Author Contributions:** CM Becker: Data collection and management, data analysis, manuscript writing and editing; M Möllers: Project development, data collection and management, manuscript writing and editing; M Danzer: Data analysis, manuscript editing; A Kuper: Data collection and management, manuscript editing; K Oelmeier: Data collection and management, manuscript editing; R Schmitz: Data collection and management, manuscript editing; D Willy: Project development, data collection and management, data analysis, manuscript writing and editing. All authors read and approved the final manuscript.

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## Data Availability

All data supporting the findings of this study are shown in the manuscript. Additional data are available upon request.

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## Figures

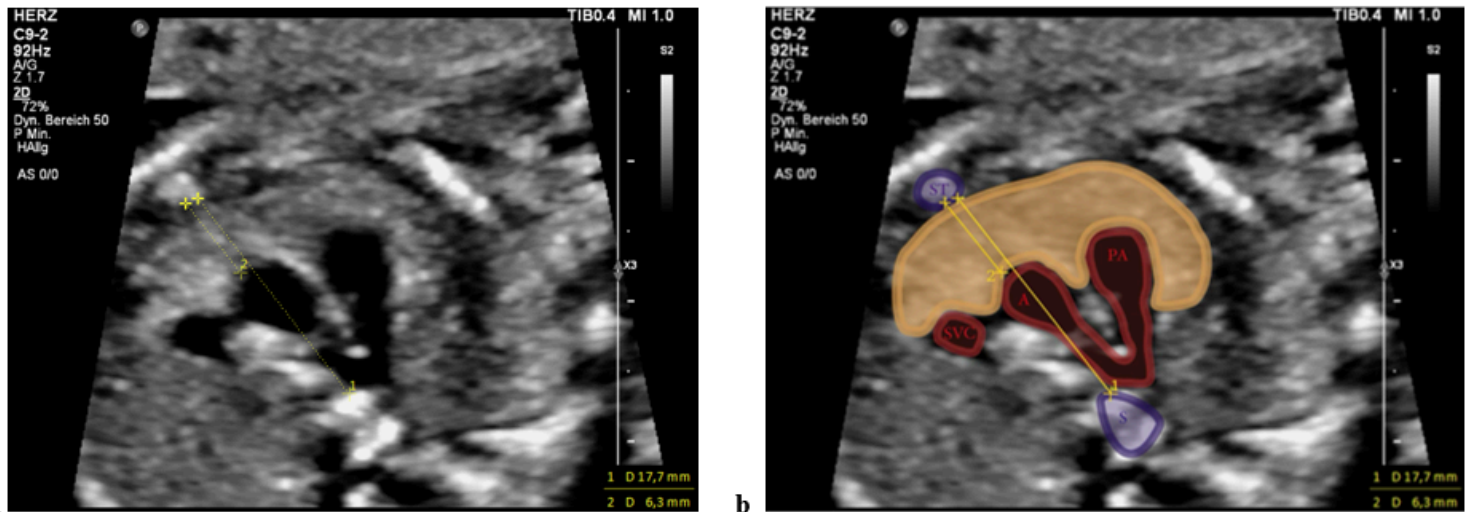


**Figure 1**

(a) Example of a measurement of the thymic-thoracic ratio (TTR) in the three vessel and trachea (3VT) view (b) schematic representation of the landmarks. PA: pulmonary artery, A: aorta, SVC: superior vena cava, S: spine, ST: sternum, 1: intrathoracic mediastinal diameter, 2: anteroposterior thymic diameter.

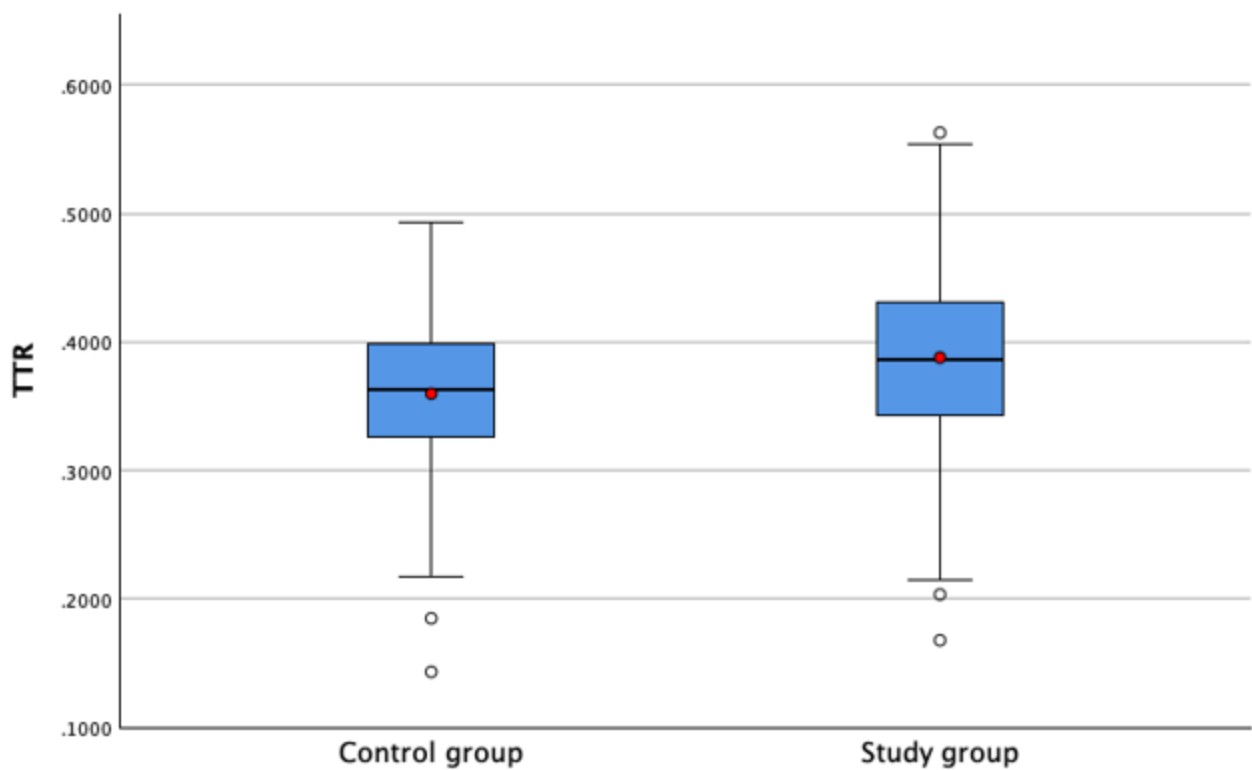


**Figure 2**

Boxplots showing the TTR across the study and control group. TTR was statistically higher in the study group than in the control group (t-test,  $p < 0.001$ ). TTR = thymic-thoracic ratio, red dots indicate means.

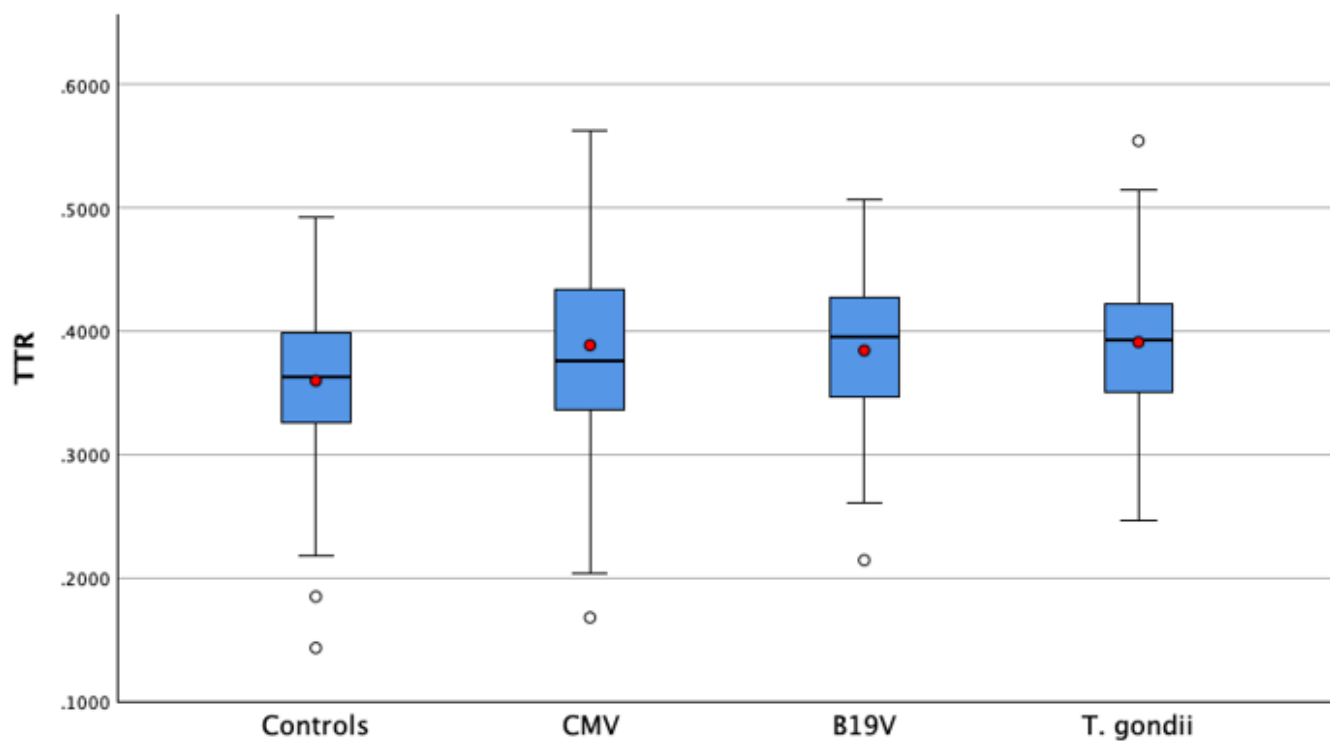


**Figure 3**

Distribution of the TTR stratified by pathogens and compared with the controls. Group differences were assessed using one-way ANOVA, followed by a Games-Howell post hoc test. A significant difference was detected between CMV and the controls (Games-Howell post hoc,  $p=0.008$ ). TTR=thymic-thoracic ratio, CMV=Cytomegalovirus, B19V=Parvovirus B19, T. gondii =Toxoplasma gondii, red dots indicate means.

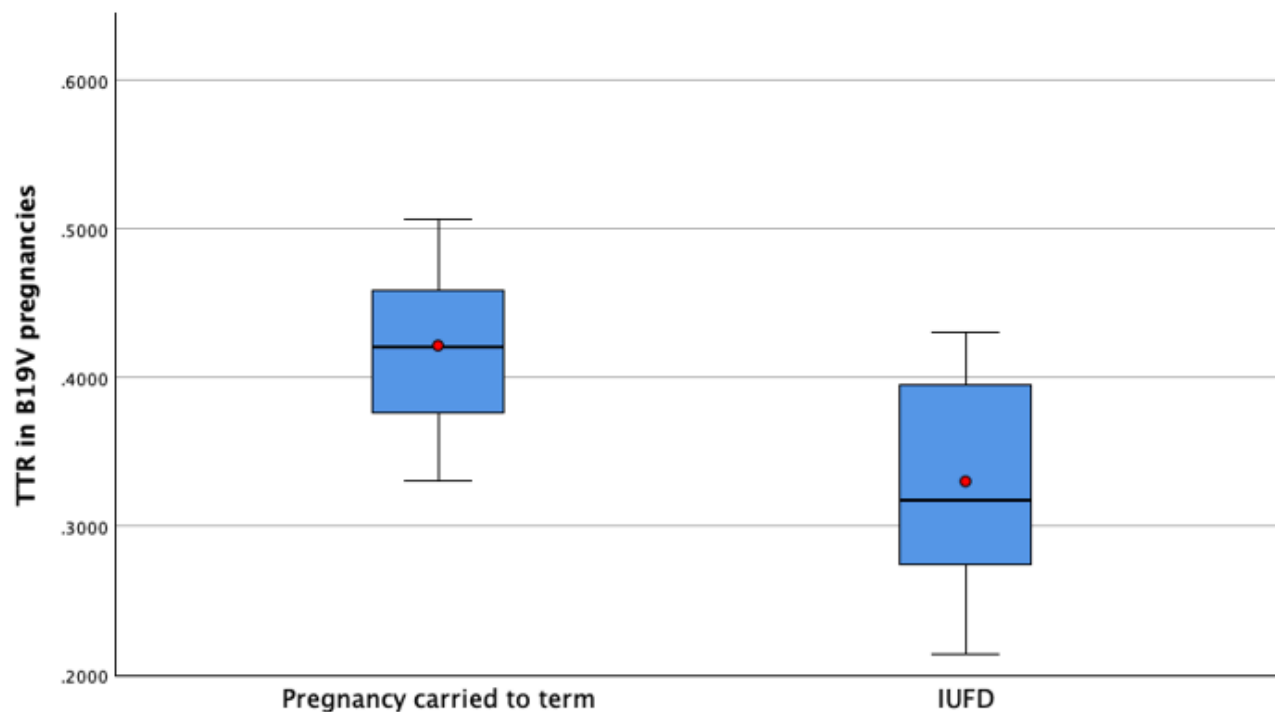


**Figure 4**

Boxplots of the TTR in pregnancies with maternal B19V-infection grouped by pregnancy outcome. Pregnancies with unknown outcome and terminations of pregnancy (TOP) are not displayed. A t-test revealed a lower TTR in the IUFD group ( $0.330 \pm 0.073$  vs  $0.422 \pm 0.052$ ,  $p < 0.001$ ). TTR=thymic-thoracic ratio, IUFD=intrauterine fetal death, B19V=Parvovirus B19, red dots indicate means.