Original paper

# Placental infectious villitis versus villitis of unknown etiology

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To assess the incidence, diagnosis, pathogenesis, and clinical and placental associations of congenital cytomegalovirus infection, 34 cases thereof diagnosed by placental/fetal or neonatal workup (group 1), and 494 placentas with villitis of unknown etiology (group 2) were extracted from a 6083-case placental database. 28 clinical and 47 placental phenotypes were compared between the two groups by Yates $\chi^2$ or ANOVA using the Bonferroni correction. 26 group 1 cases did and 8 did not feature placental villitis, but all cases were positive as shown by immunohistochemistry and/or *in situ* hybridization. Only 5 differences were statistically significant (p Bonferroni $< 0.0056$): gestational age 29.8 $\pm$6.5 vs. 35.5 $\pm$4.9 weeks, perinatal mortality 67.6 vs. 16.2%, nonmacerated stillbirth 20.6 vs. 3.0%, macerated stillbirth 38.2 vs. 9.3%, and diffuse villous fibrosis 44.1 vs. 12.5%, between group 1 and group 2, respectively. The absence of significant differences in placental phenotypes between group 1 and group 2 other than the histological pattern of villitis indicates that not the cytomegalovirus villitis but the direct viral cytopathogenic effect on fetal organs makes the difference in the dire clinical outcome in the former. As about a third of cytomegalovirus infections show no villitis, the combination of the clinical picture and placental patterns creates the best chance to detect congenital cytomegalovirus infection.

**Key words:** cytomegalovirus, placenta, villitis, villitis of unknown etiology, perinatal morbidity, perinatal mortality.

## Introduction

Perinatal infection is the major cause of perinatal mortality and morbidity. It is frequently associated with placental inflammation. The recurrence rate of placental inflammation, either acute or chronic, is higher than that of hypoxic and thrombotic placental lesions [1]. The amniotic sac infection syndrome associated with acute chorioamnionitis and caused by the acute bacterial ascending infection is the most common single cause of perinatal mortality, particularly in the 2nd trimester [2].

The role of chronic villitis in perinatal morbidity and mortality cannot be overemphasized. It may be of infectious origin (viral, bacterial), or, most commonly, of yet unknown etiology (VUE). If high grade, VUE may be recurrent and associated with perinatal pathology such as recurrent reproductive loss, fetal growth restriction (FGR), preterm birth, long-term neurological impairment, and cerebral palsy [3, 4, 5, 6, 7, 8, 9, 10]. The mechanism of villous damage in VUE is the maternal anti-fetal immune reaction resembling allograft rejection, as it histologically features the inflammatory infiltrate containing predominantly maternal T-lymphocytes [11]. The fetal morbidity is therefore most likely secondary to placental pathology. Histologically, VUE features lymphohistiocytic infiltrate of agglutinated

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chorionic villi with spillage of inflammation into the intervillous space, stem vessel microangiopathy with thrombosis and frequently decidual lymphohistiocytic inflammation [4, 5, 6].

TORCH infections are major contributors to prenatal, perinatal, and postnatal morbidity and mortality, particularly in low-income and middle-income countries [12]. Congenital cytomegalovirus (CMV) infection is the most common of those [13] and is responsible for numerous perinatal complications such as perinatal mortality, preterm birth, fetal growth restriction, hydrops fetalis, congenital anomalies, neonatal gastrointestinal complications, cerebral hemorrhage, permanent neurological deficits, hearing loss, and visual impairment [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25]. Maternal primary CMV infection is diagnosed in pregnancy based on maternal seroconversion in the 1st trimester. Fetal infection can be diagnosed in the 2nd trimester by PCR for CMV DNA of amniotic fluid. Antenatal fetal imaging in the 3rd trimester is prognostic for the degree of the offspring involvement. Since most infections are asymptomatic and not all women are screened, placental examination is useful for detection of infection in stillbirths and unsuspected neonatal infections [26, 27]. Focal segmental lymphoplasmacytic villitis [28, 29], if present, is characteristic for placental CMV involvement and is usually histologically different from VUE although placental involvement by CMV may not be seen on routine hematoxylin-eosin stained slides. CMV villitis shows dispersed inflamed villi instead of grouping/agglutination seen in VUE. Although the lymphohistiocytic inflammatory infiltrate is seen in CMV villitis, it not as dense as in VUE. Villous plasma cells are not usually seen in VUE as opposed to CMV villitis, the presence of plasma cells and hemosiderin deposition virtually pathognomonic of CMV infection [4]. Villous edema, necrotizing villitis, sclerosis of villous capillaries, chorionic vessel thrombosis, granulomatous villitis in early stage and fibrosis in late stage, and normoblastemia may dominate the histological picture. Finally, microthrombotic vasculopathy is more common in VUE than CMV villitis. Viral inclusions are seen in only 10% of cases of fetal infection [27]. Sometimes CMV villitis can masquerade as VUE [5]. Villous damage in congenital CMV infection is initiated by the primary trophoblastic injury by the virus [22]. Some authors claim that secondary uteroplacental insufficiency and hypoxia are responsible for the clinical presentation of CMV infection [16, 30], particularly in FGR, regardless of virus transmission to the fetus [15, 22]. As placental examination is the primary tool for evaluation of both perinatal infections and in-utero hypoxia, this study aims to retrospectively compare frequencies of other patterns of placental injury, in particular hypoxic, in placental CMV involvement and VUE.

## Material and methods

The study was approved by the Institutional Review Board (#2016-7942). 6083 consecutive placentas, gestational age 15-42 weeks, were examined by the author in four tertiary care institutions on three continents in the period 1994-2016. The placentas were submitted for examination at the discretion of obstetricians because of high risk pregnancy, operative delivery or grossly abnormal placenta. The placentas were grossed, stained and diagnoses were made as in the author's previous publications [9, 31]. In 34 cases, congenital CMV infection was diagnosed by placental/fetal or neonatal workup (group 1), and 494 cases showed VUE (group 2).

Placental involvement by CMV infection has been typically made by histological diagnosis of focal segmental lymphoplasmacytic villitis [28, 29], with additional histological features as described above and depicted in Fig. 1, and confirmed by positive immunohistochemistry or *in situ* hybridization on placental tissue [4, 5, 6, 17] (Figs. 1 and 2). In selected cases E-cadherin/CD34 immunohistochemistry was performed to detect the incipient fetal malperfusion of fetal thrombotic vasculopathy, and highlighting the histological features of chronic hypoxic placental injury [32, 33] and immunofluorescence for X and Y chromosomes was performed in selected cases to confirm the origin of inflammatory cells (maternal versus fetal) [29]. The diagnosis of VUE was made based on the presence of lymphohistiocytic villitis involving groups of at least 3 chorionic villi with a tendency to agglutinate together, with blurring of contours thereof, hypovascularity/avascularity, and spilling of inflammatory infiltrate into the intervillous space [3, 4, 5, 6] (Figs. 1 and 2), and no clinical or pathological evidence of infectious etiology. Twenty-eight clinical and 47 placental phenotypes were compared between groups 1 and 2 by Yates $\chi^2$ or ANOVA using the Bonferroni correction for multiple comparisons.

## Results

Twenty-six CMV cases did show chronic focal segmental lymphoplasmacytic villitis and 8 CMV cases did not. All the latter 8 cases were positive for CMV according to placental immunohistochemistry (IHC) or in situ hybridization (ISH) and all were associated with perinatal mortality (4 neonatal deaths, 2 nonmacerated stillbirths and 2 macerated stillbirths). One case showed FGR, 1 case had congenital malformation, 4 cases showed acute chorioamnionitis, 1 case showed villous edema, 2 cases showed preuterine pattern of chronic hypoxic placental injury, and 1 case showed plasma cell deciduitis. In only 5 of cases with lymphoplasmacytic villitis was a typical CMV cytopathogenic effect observed in chorionic villi (owl-

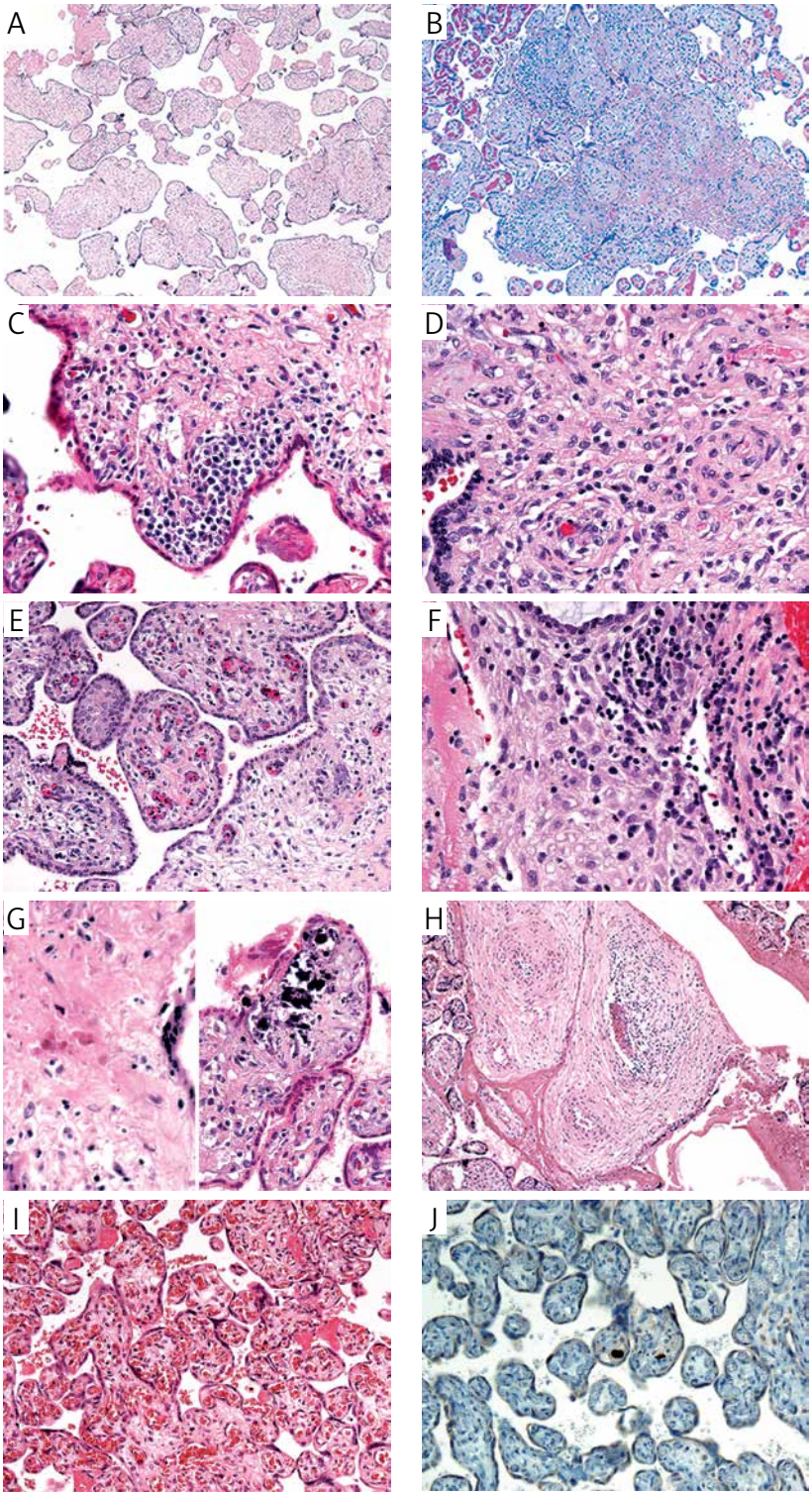


**Fig. 1.** Placental cytomegalovirus involvements versus villitis of unknown etiology. Objective magnifications are given in parentheses. A) Cytomegalovirus placentitis, low power magnification, fetal death, 24 weeks, diffuse villous fibrosis of isolated chorionic villi (magnification 10×). B) Villitis of unknown etiology, 32 weeks (magnification 10×), agglutination of inflamed chorionic villi. C) Focal segmental cytomegalovirus lymphoplasmacytic villitis, fetal death at 23 weeks (magnification 40×). D) Lymphohistiocytic villitis of unknown etiology, 31 weeks, CHAOS (magnification 40×). E) Cytomegalovirus inclusions and erythroblastosis, fetal death at 23 weeks (magnification 40×). F) Chronic deciduitis with plasma cells in a case with villitis of unknown etiology, same case as D, (magnification 40×). G) Cytomegalovirus infection, same as in C (magnification 40×), hemosiderin deposition (left) and calcification (right). H) Stem villous involvement with villitis of unknown etiology with a mural thrombus, 40 weeks, s/p cerclage (magnification 10×). I) Preuterine pattern of hypoxic injury, 35 weeks, no features of CMV infection, neonatal death a 1 month (magnification 20×). J) Same case as I, CMV immunohistochemistry (magnification 20×)

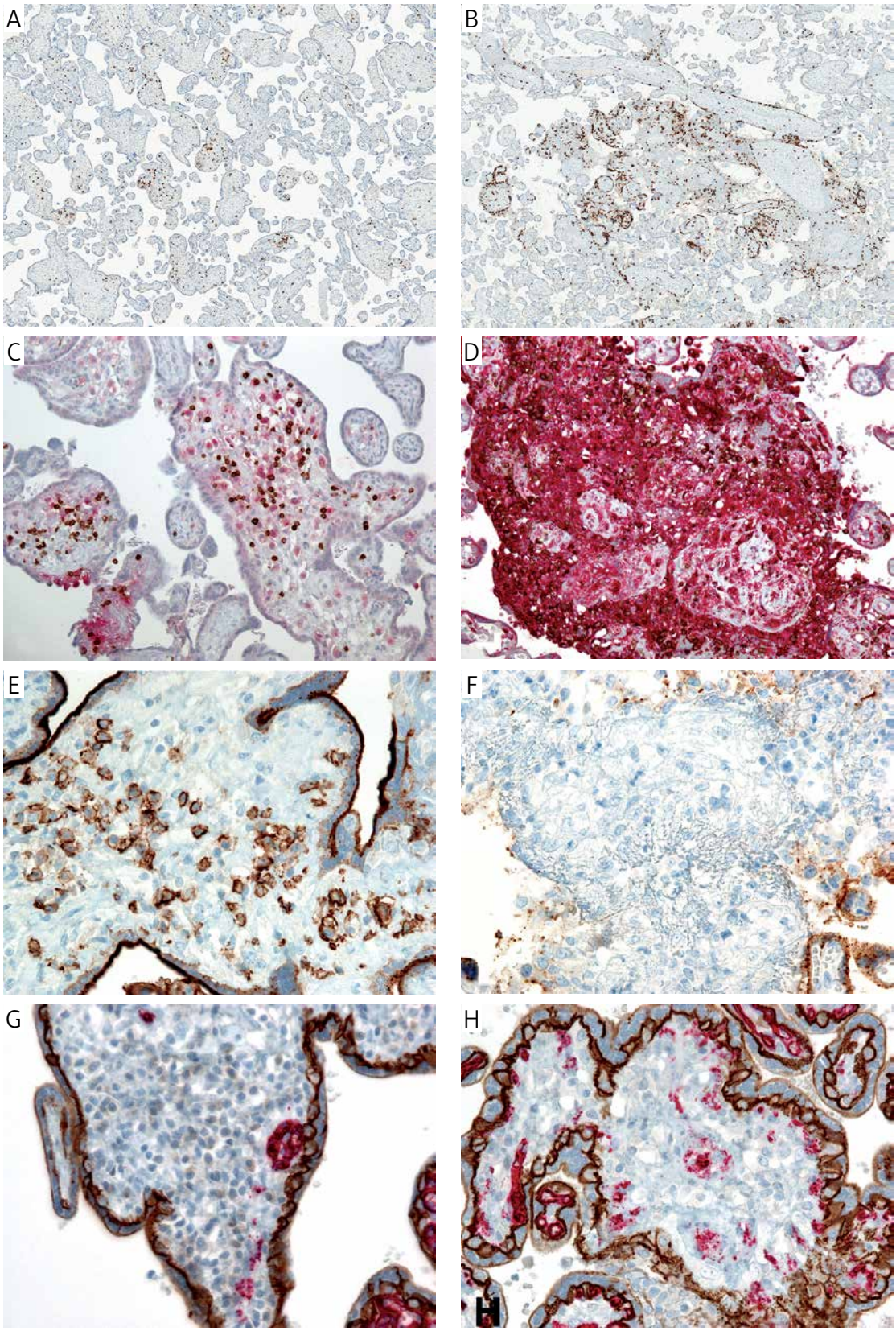


**Fig. 2.** Immunohistochemistry in CMV villitis and VUO. Objective magnifications are given in parentheses. A) CMV villitis, 23 weeks, stillbirth, CD8 (magnification 4×). B) Villitis of unknown etiology, twin A after IVF, stillbirth with TF and CDH at 34 weeks, CD 8 (magnification 4×). C) Same case as A, CD3/CD68 (magnification 20×). D) Same case as B, CD3/CD68 (magnification 20×). E) Same case as A, CD138 (magnification 40×). F) Same case as B, CD138 (magnification 40×). G) Same case as A, E cadherin/CD34 (magnification 40×). G) Villitis of unknown etiology, 31 weeks, CHAOS, E cadherin/CD34 (magnification 40×)

eye nuclear inclusions and cytoplasmic inclusions). In cases of VUE, CMV *in situ* hybridization or immunohistochemistry was sporadically performed and was negative.

The differences in 9 clinical or placental phenotypes were statistically significant ($p < 0.05$): gestational age, cesarean sections, perinatal mortality, macerated stillbirths, nonmacerated stillbirths, placental weight, villous edema, luminal vascular abnormalities of chorionic villi, and diffuse villous fibrosis between all 34 CMV cases and VUE cases, respectively. After Bonferroni correction, only 5 differences remained statistically significant (p Bonferroni $< 0.0056$): gestational age 29.8 ±6.5 vs. 35.5 ±4.9 weeks, perinatal mortality 73.5 vs. 16.2%, nonmacerated stillbirth 17.6 vs. 3.0%, macerated stillbirth 41.2 vs. 9.3%, and diffuse villous fibrosis 44.1 vs. 12.5%, in group 1 and group 2 respectively. The average gestational age in CMV cases was 30 weeks, two weeks shorter than the corresponding median placental weight, possibly due to the relatively high percentage of placental edema in CMV placentas (15%). 15% of offspring featured congenital malformations. The majority of the remaining 28 clinical and 48 placental phenotypes did not differ from the averages of the author's clinicoplacental database [31] (Table I).

## Discussion

The author has confirmed that the CMV infection in pregnancy is devastating. In the author's placental material there is no other phenotype that is associated with such high perinatal mortality as placental involvement by CMV infection presented in this analysis. Moreover, abnormal clinical phenotypes and outcomes other than perinatal mortality are conspicuously more less frequent than in the author's total placental database [31], and also in comparison with VUE, which in our material clustered with hypertensive conditions of pregnancy, oligohydramnios, and abnormal fetal heart rate tracings [31] (Table I). The VUE complications in this material were generally lower than those quoted in the literature [4, 5, 6, 11], most likely because of inclusion of also milder cases of VUE in the current series. Although only high grade VUE is associated with adverse perinatal outcomes, we did not apply the recently recommended grading of VUE into low grade and high grade [3] as the material includes cases also signed out by me in several hospitals over 22 years and slides are not available for me for re-review. The Cesarean section rate twice as low in group 1 than in group 2 and lower than the overall cesarean section rate in our placental material is most likely due to the high stillbirth rate in group 1, in which Cesarean sections are rarely performed. The average gestational age in group 1 was 30 weeks, i.e. 6 weeks shorter than the average in group 2, the latter characteristically more common in the 3rd trimester, and particularly at term pregnancy [10].

Since in documented fetal infection the placenta may show no villitis, placental involvement by CMV may be revealed by in situ hybridization and/or immunohistochemistry, like in all 8 cases in the present series. The percentage of "normal" histology could be even higher, as many cases, particularly asymptomatic, may not be diagnosed clinically and may not have placental examination. Unfortunately, those cases may also have unfavorable outcomes: 10-15% of initially asymptomatic newborns develop neurodevelopmental damage within the first three years of life [34] and approximately 5-20% of newborns with maternal primary infection are overtly symptomatic at birth: mortality 5%, 50-60% of survivors develop severe long-term neurologic morbidity [35, 36], and delayed neonatal sequelae of CMV infection may strike without warning. This analysis confirmed that ISH and IHC are more sensitive than routine histology. CMV exposure in utero by PCR on formalin-fixed, paraffin-embedded placental tissue may also be a useful adjunct to histologic evaluation and may identify even more infants requiring close clinical follow-up [37]. Other chronic villitides (Fig. 3) may show a characteristic histology such as patchy scattered villous necrosis of HSV [38] (A, B), chronic otherwise nonspecific villitis with cysts of toxoplasma gondii (G-H), or lymphoplasmacytic villitis of Zika infection [39]. Some TORCH infections may feature no villitis, like in syphilis infection (C, D) or parvovirus infection with its intravascular lantern cells, or HIV infection (E, F). In granulomatous villitis (I) and eosinophilic T cell vasculitis infectious etiology is usually not found.

Like clinical phenotypes, CMV villitis featured conspicuously uncommon other abnormal placental phenotypes, statistically not significantly different from VUE. The most common statistically significant placental histological feature was diffuse placental fibrosis, but the high rate of macerated stillbirth might have accounted for that and not necessarily the focal segmental villous fibrosis of the CMV placentitis. Median placental weight, possibly due to the relatively high percentage of placental edema in CMV placentas (15%), was two weeks higher than expected for the gestational age (Table I). Although postmortem regressive changes could have potentially interfered with placental diagnosis in group 1, the estimate of the degree of villous maturity/hypermaturity was still possible, as villous size is not affected by postmortem fibrosis. Also, we generously used the iron stain and/or E cadherin/CD34 immunostain to reveal potentially hidden clusters of hemosiderotic/hypovascular villi of fetal thrombotic vasculopathy present before fetal death [28, 32, 33].

**Table I.** Frequencies of clinical and placental phenotypes in group 1 and group 2

| | Group 1 Cytomegalovirus infection | Group 2 Villitis of unknown etiology | Yates $\chi^2$ or F | p |
|---|---|---|---|---|
| Number of cases | 34 | 494 | | |
| ***Clinical variables*** | | | | |
| **Gestational age (weeks, average ± standard deviation)** | **29.8 ±6.5** | **35.5 ±4.9** | **39.417** | **7.1E-10** |
| Poor or absent prenatal care | 1 (2.9%) | 28 (5.7%) | | |
| Substance abuse | 4 (11.8%) | 41 (8.3%) | | |
| Gestational hypertension | 0 | 16 (3.2%) | | |
| Preeclampsia | 1 (2.9%) | 53 (10.7%) | | |
| Mild | 0 | 25 (5.1%) | | |
| Severe | 1 (2.9%) | 22 (4.4%) | | |
| HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) | 0 | 5 (1%) | | |
| Eclampsia | 0 | 1 (0.2%) | | |
| Chronic hypertension (including superimposed preeclampsia) | 2 (5.9%) | 18 (3.6%) | | |
| Maternal diabetes mellitus | 2 (5.9%) | 45 (9.1%) | | |
| Oligohydramnios | 5 (14.7%) | 26 (5.3%) | | |
| Polyhydramnios | 0 | 19 (3.8%) | | |
| Premature rupture of membranes | 4 (11.8%) | 51 (10.3%) | | |
| Antepartum hemorrhage | 2 (5.9%) | 54 (10.9%) | | |
| Meconium (clinical) | 3 (8.8%) | 47 (9.5%) | | |
| Thin | 3 (8.8%) | 45 (9.1%) | | |
| Thick | 0 | 2 (0.4%) | | |
| Abnormal fetal heart rate tracing[a] | 3 (8.8%) | 103 (20.8%) | | |
| Abnormal umbilical artery Dopplers | 2 (5.9%) | 12 (2.4%) | | |
| Induction of labor | 3 (8.8%) | 54 (10.9%) | | |
| Cesarean section | 7 (20.6%) | 199 (40.3%) | 4.39 | 0.036 |
| **Perinatal mortality** | **25 (73.5%)** | **80 (16.2%)** | **62.09** | **0** |
| Neonatal | 5 (14.7%) | 17 (3.4%) | 7.48 | 0.006 |
| **Nonmacerated stillbirth** | **6 (17.6%)** | **15 (3.0%)** | **14.16** | **0.00017** |
| **Macerated stillbirth** | **14 (41.2%)** | **46 (9.3%)** | **28.98** | **7e-8** |
| Multiple pregnancy | 2 (5.9%) | 31 (6.3%) | | |
| Fetal growth restriction[b] | 4 (11.8%) | 76 (15.4%) | | |
| Umbilical cord compromise[c] | 2 (5.9%) | 31 (6.3%) | | |
| Congenital malformations | 5 (14.7%) | 44 (8.9%) | | |
| Abnormal 3rd stage of labor (prolonged, hemorrhage) | 1 (2.9%) | 28 (5.7%) | | |
| *Placental variables* | | | | |
| Placental weight (grams, average ± standard deviation) | 315 ±199 | 402 ±181 | 7.19 | 0.007757 |

**Table I.** Cont.

| | Group 1 Cytomegalovirus infection | Group 2 Villitis of unknown etiology | Yates $\chi^2$ or F | p |
|---|---|---|---|---|
| Acute chorioamnionitis | 13 (38.2%) | 184 (37.2% | | |
| Maternal inflammatory response | 12 (35.3%) | 147 (29.7%) | | |
| Fetal inflammatory response | 1 (2.9%) | 37 (7.5%) | | |
| Plasma cell deciduitis | 3 (8.8%) | 38 (7.7%) | | |
| Erythroblastosis of fetal blood | 6 (17.6%) | 51 (10.3%) | | |
| Meconium (histological) | 8 (23.6%) | 192 (38.9%) | | |
| Deep (decidual) | 1 (2.9%) | 55 (11.1%) | | |
| Shallow (amnionic or trophoblastic) | 7 (20.6%) | 147 (29.6%) | | |
| Villous infarction (> 5% of placental parenchyma) | 4 (11.8%) | 57 (11.5%) | | |
| Hypertrophic decidual arteriolopathy | 4 (11.8%) | 95 (19.2%) | | |
| Atherosis of spiral arterioles | 0 | 22 (4.4%) | | |
| Laminar necrosis of membranes[d] | 3 (8.8%) | 94 (19.0%) | | |
| Patterns of diffuse hypoxic injury | 4 (11.8%) | 60 (12.1%) | | |
| Preuterine | 3 (8.8%) | 20 (4.0%) | | |
| Uterine | 0 | 33 (6.7%) | | |
| Postuterine | 1 (2.9%) | 7 (1.4%) | | |
| Membrane microscopic chorionic pseudocysts[e] | 1 (2.9%) | 42 (8.5%) | | |
| Chorionic disc microscopic chorionic pseudocysts[f] | 1 (2.9%) | 32 (6.5%) | | |
| Maternal floor multinucleate trophoblastic giant cells | 2 (5.9%) | 32 (6.5%) | | |
| Excessive amount of extravillous trophoblasts in chorionic disc | 1 (2.9%) | 28 (5.7%) | | |
| Massive perivillous fibrin deposition (> 30% of placental parenchyma) | 2 (5.9%) | 49 (9.9%) | | |
| Chorangiosis | 1 (2.9%) | 57 (11.5%) | | |
| Obliterative endarteritis | 0 | 21 (4.2%) | | |
| Intervillous thrombus | 2 (5.9%) | 69 (14.0%) | | |
| Retroplacental hematoma | 2 (5.9%) | 25 (5.1%) | | |
| Intravillous hemorrhage | 0 | 7 (1.4%) | | |
| Choriodecidual hemosiderosis | 2 (5.9%) | 21 (4.2%) | | |
| Villous edema | 5 (14.7%) | 23 (4.7%) | 4.55 | 0.033 |
| Lobular villous hemosiderosis | 1 (2.9%) | 13 (2.6%) | | |
| Luminal vascular abnormalities of chorionic villi | 10 (29.4%) | 62 (12.5%) | 6.31 | 0.012 |
| **Diffuse villous fibrosis** | **15 (44.1%)** | **62 (12.5%)** | **22.98** | **0.0000016** |
| Fetal vascular thrombi | 2 (5.9%) | 49 (9.9%) | | |
| Cluster(s) of at least 3 avascular chorionic villi | 3 (8.8%) | 72 (14.6%) | | |
| Hemorrhagic endovasculitis | 4 (11.8%) | 40 (8.1%) | | |
| Intimal cushions in stem/chorionic veins | 1 (2.9%) | 27 (5.5%) | | |
| Two-vessel umbilical cord | 0 | 15 (3.0%) | | |

**Table I.** Cont.

| | Group 1 Cytomegalovirus infection | Group 2 Villitis of unknown etiology | Yates $\chi^2$ or F | p |
|---|---|---|---|---|
| Hypercoiled umbilical cord | 1 (2.9%) | 42 (8.5%) | | |
| Hypocoiled umbilical cord | 0 | 20 (4.0%) | | |
| Perivascular stem edema | 0 | 42 (8.5%) | | |
| Marginal insertion of umbilical cord | 4 (11.8%) | 40 (8.1%) | | |
| Velamentous insertion of umbilical cord | 1 (2.9%) | 15 (3.0%) | | |
| Other umbilical cord abnormalities[g] | 3 (8.8%) | 56 (11.3%) | | |
| Placenta creta (including basal plate myometrial fibers) | 0 | 23 (4.7%) | | |
| Amnion nodosum/chorion nodosum | 0 | 12 (2.4%) | | |
| Marginate or vallate placenta | 2 (5.9%) | 30 (6.1%) | | |
| Gross chorionic cyst(s) | 2 (5.9%) | 9 (1.8%) | | |
| Succenturiate lobe | 0 | 19 (3.8%) | | |
| Chorangioma | 1 (2.9%) | 6 (1.2%) | | |
| Dilatation of fetal veins | 0 | 25 (5.1%) | | |

*Bold font, statistically significant differences after Bonferroni correction for multiple comparisons ($p < 0.005$)*
*[a]abnormal non-stress test and/or abnormal contraction stress test and/or abnormal intrapartum cardiotocography (prolonged bradycardia and/or prolonged tachycardia and or decrease of fetal heart rate variability and/or late decelerations)*
*[b]birth weight <10 centile*
*[c]variable decelerations, encirclement, true knot, or prolapse*
*[d]at least 10% of membrane rolls*
*[e]at least 3 pseudocysts per membrane roll*
*[f]at least 3 pseudocysts per section of grossly unremarkable chorionic disc*
*[g]too long, too short, too thin, stricture, aneurysm, varix, hematoma, vessel unprotected by Wharton jelly, chorda, ulcer, barber pole funisitis, amniotic band, meconium toxicity, marginal insertion, velamentous insertion, furcate insertion, edema*

Although some authors have posited that uteroplacental insufficiency and hypoxia have a harmful effect in CMV infection [16, 30], this analysis did not support this hypothesis, as acute and chronic hypoxic placental lesions/patterns were not more common in the CMV-infected placentas than in the authors' placental database in general [31] and in the VUE in particular (Table I). Moreover, in 8 group 1 cases without visible CMV placental involvement on hematoxylin-eosin stained slides the pregnancy outcome was as dismal as in cases with CMV villitis, all 8 cases featuring perinatal mortality. The conspicuous absence of significant differences in hypoxic placental phenotypes between the placental involvement by CMV infection and VUE cannot be explained by a different pathomechanism of both inflammatory patterns of placental injury, infectious in the former and immunologic (host vs. graft) in the latter. In CMV villitis FISH for sex chromosomes performed on formalin-fixed and paraffin-embedded placental tissue of male fetuses showed predominantly fetal inflammatory cells in CMV infection and maternal inflammatory cells in VUE (Fig. 4) [29]. Therefore, it appears that likely not the CMV villitis itself but rather a direct viral cytopathogenic effect on other fetal organs causes the damage. The villous cytotrophoblasts damaged by CMV may only facilitate the entry of the virus into the fetal compartment [40], but damage to the fetus does not appear to be hypoxic/uteroplacental as some authors claim.

The limitation of the study is its retrospective nature, e.g. only 3 representative paracentral blocks of placental tissue were taken for histological examination in cases without gross lesions, which had been shown to identify only 62% of villitis [41]. One may assume that a similar situation can happen with CMV villitis, particularly as in 8 of 34 cases no villitis was present in placental CMV involvement. The strength of the study was consistently studying large numbers of clinical and placental phenotypes in that selection of material, which to our knowledge has been performed for the first time.

In summary, our results do not support the hypothesis of placental insufficiency/hypoxic cause of fetal morbidity/mortality in congenital CMV infection. Nevertheless, the CMV-infected placentas portend very poorly for the pregnancy and the combination of the clinical picture and placental histology creates the best chance to detect congenital CMV infection.

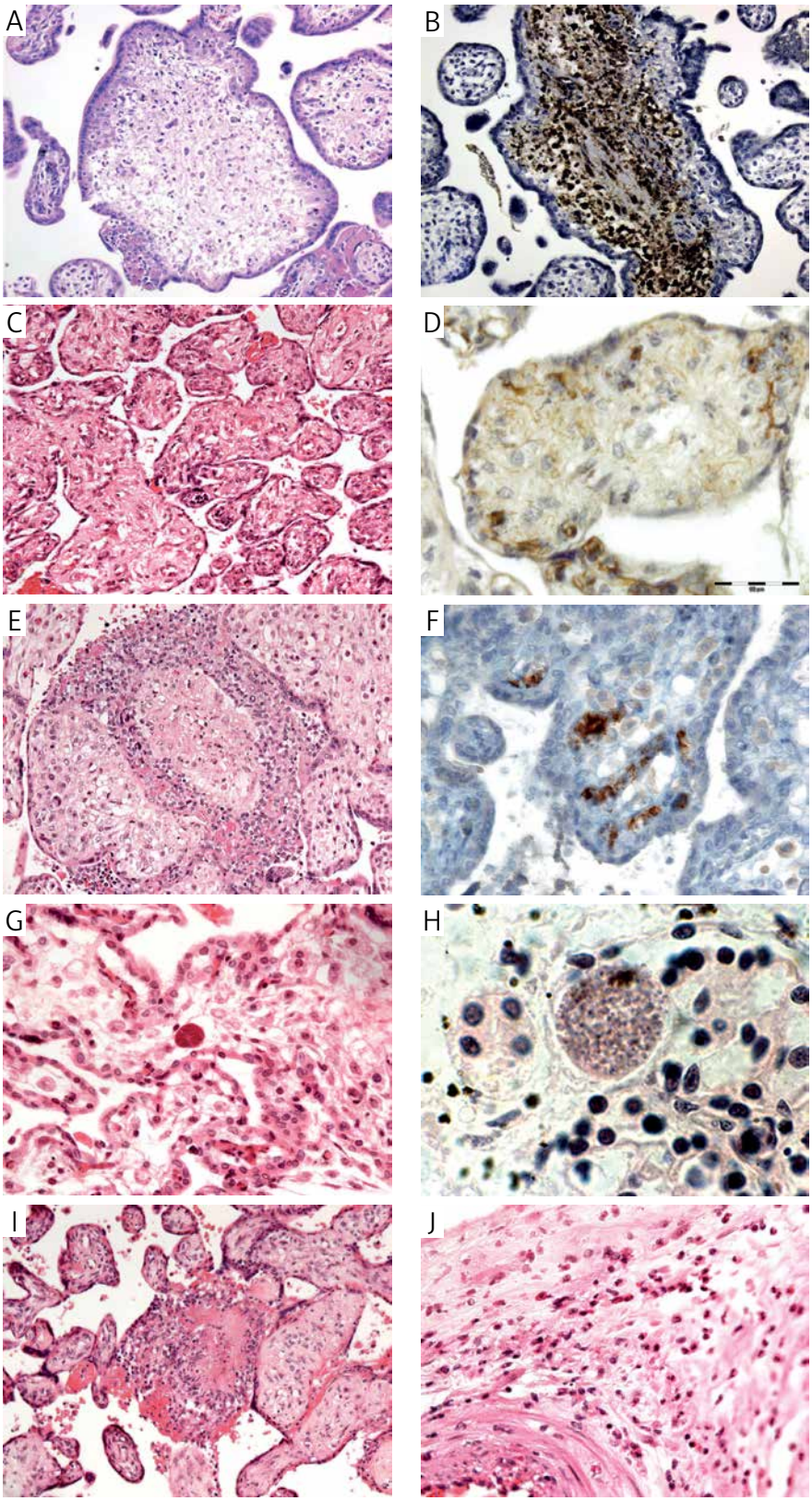


**Fig. 3.** Other infectious and noninfectious villitides. A) Herpes simplex infection, bland villous necrosis, monoamniotic monochorionic twins, missed abortion at 15 weeks (magnification 20×). B) Same case as A, HSV immunohistochemistry (magnification 20×); C) Congenital syphilis, 32 weeks (magnification 20×). D) Same case as C. Treponema immunohistochemistry (magnification 40×). E) HIV infection, stillbirth at 23 weeks, no villitis (magnification 20×). F) Same case as E, p24 immunohistochemistry (magnification 40×). G) Toxoplasma villitis, 40 weeks, neonatal death (magnification 40×). H) Same case as G (toxoplasma cyst (magnification 100×). I) Granulomatous villitis, stillbirth at 25 weeks (magnification 20×). J) Eosinophilic T cell vasculitis of chorionic plate PROM at 37 weeks (magnification 40×)

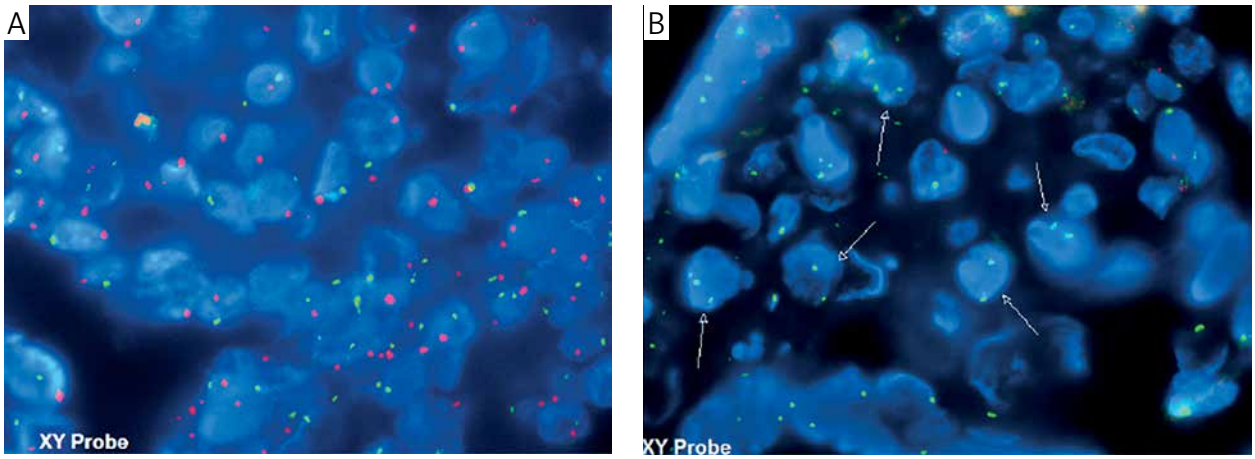


**Fig. 4.** FISH for A (green) and Y (red) chromosomes in male fetuses (magnification 100×). A) cytomegalovirus villitis and B) villitis of unknown etiology [29]

*The author declares no conflict of interest.*

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