Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 13 November 2017 | doi:10.4414/smw.2017.14534
Cite this as: Swiss Med Wkly. 2017;147:w14534

Ultrasound indications for maternal STORCH testing in pregnancy

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Summary

AIMS OF THE STUDY: Fetal abnormalities found on ultrasonography lead to a variety of diagnostic procedures, including a panel of serologies to detect possible maternal STORCH infections encompassing syphilis, *Toxoplasma gondii*, rubella, cytomegalovirus, herpes simplex, and others (human immunodeficiency virus, hepatitis B and C, parvovirus B19, enterovirus, varicella zoster, and *Leptospira interrogans*). The value of indiscriminate testing for infections upon the detection of fetal ultrasound abnormalities has been questioned. The aim of this study was to review the ultrasonographic abnormalities leading to maternal STORCH panels at the obstetrics department of a university hospital.

METHODS: Laboratory results of all maternal STORCH tests requested after the detection of ultrasonographic abnormalities during a 5-year period (2008–2012) were analysed. The main ultrasound findings possibly caused by congenital infection were noted, and the outcomes of confirmed maternal and fetal infections were studied.

RESULTS: In our study period, 392 maternal STORCH tests were performed because of fetal ultrasound abnormalities. The most common findings leading to STORCH testing were intrauterine growth restriction (30.4%) including microcephaly (1.5%), polyhydramnios (14.8%), and intrauterine fetal demise (13.3%). Maternal STORCH infections were found in 3.4% of growth-restricted fetuses, 5.2% of polyhydramnios, and 1.9% of intrauterine fetal demise. The leading aetiologies were cytomegalovirus and parvovirus B19. All seven congenital infections displayed multiple ultrasonographic abnormalities.

CONCLUSION: Ultrasonographic findings associated with fetal infection are neither sensitive nor specific. Testing for STORCH infections should take into account exposure history, clinical signs and symptoms, obstetric history, and fetal ultrasound findings, but with special attention paid to cytomegalovirus and parvovirus B19.

Key words: *STORCH, congenital infection, fetal ultrasound abnormalities, CMV*

Introduction

Materno-fetal infections may cause severe fetal disease, intrauterine fetal demise (IUFD), and long-term manifestations. The acronym TORCH was established in 1971 to describe a group of congenital infections with similar clinical features. The term initially included *Toxoplasma gondii*, others (syphilis), rubella virus, cytomegalovirus (CMV), and herpes simplex virus 1 and 2 (HSV-1, HSV-2) [1] and has since then been extended to include several other infectious agents that may cause congenital infections [2]. Most recently, the addition of zika virus should be considered in the light of its strong association with fetal microcephaly if maternal infection develops in the first trimester [3–5]. Due to the recent increase in syphilis rates, use of the term STORCH in this paper seems appropriate (the "S" denoting syphilis). The epidemiology of STORCH infections varies geographically. In low-income and middle-income countries, STORCH infections are major contributors to prenatal, perinatal, and postnatal morbidity and mortality. Cytomegalovirus infection is the most common viral infection in pregnancy, affecting 0.4 to 2.3% of live-born infants, and is more common than other well-known diseases such as Down syndrome, which affects about 1 out of 730 live born infants [6–8]. While most STORCH infections cause only mild symptoms in the mother, fetal infection has a broad spectrum of manifestations. Infection in utero may be asymptomatic or may cause severe fetal malformations, central nervous system damage, or fetal death. Affected neonates can be asymptomatic at birth, and late manifestations may become apparent only years after birth. Obvious fetal abnormalities are usually detected on routine ultrasound examinations during pregnancy and prompt a diagnostic work-up including a panel of serological tests to detect possible STORCH infections. For many years, the STORCH test has been used as a panel upon the detection of various ultrasound findings, and during recent decades, questions have been raised concerning the indi-

Author contributions
Both authors Cora Voekt and Therese Rinderknecht contributed equally to this work as first authors.

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cations and cost-effectiveness of STORCH testing [9–11]. The aim of this study was to review the ultrasound indications for STORCH panels at the university hospital of Basel during a five-year period.

Materials and methods

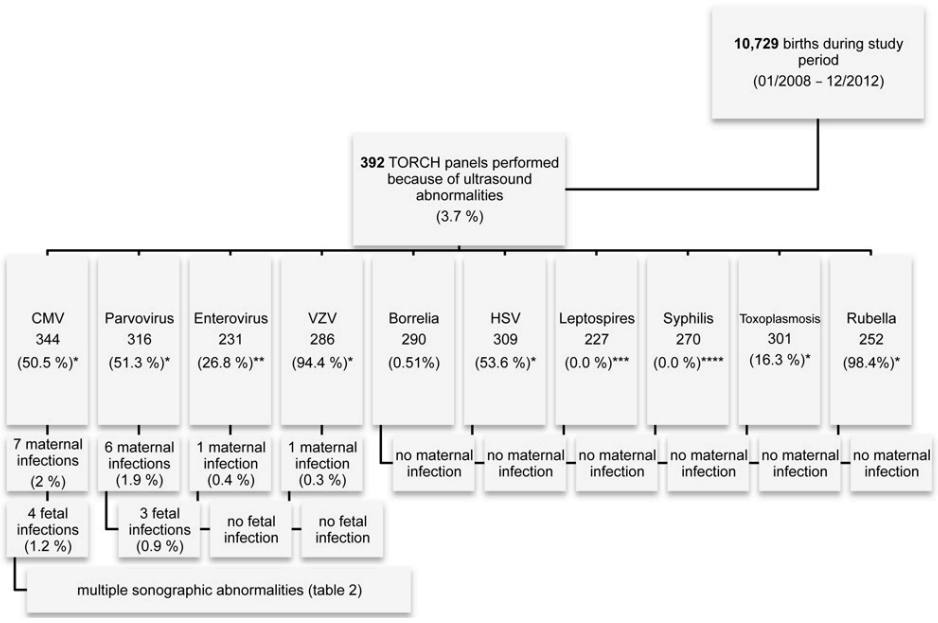
Practice at the University Women's Hospital in Basel during the time period of this study included routine screening in every pregnancy for human immunodeficiency virus (HIV) infection, syphilis, and hepatitis B, checking for anti-varicella zoster virus (VZV), IgG antibodies if prior varicella infection could not be confirmed by the patient, and verifying rubella vaccinations by checking anti-rubella antibodies. Routine screening for toxoplasmosis was stopped about two years into the study period according to the revised national guidelines [12]. Testing for any other STORCH agents is requested for specific indications only and includes serologies for *Borrelia burgdorferi*, cytomegalovirus, herpes simplex virus, *Toxoplasma gondii*, parvovirus B19, enterovirus, and leptospires. Laboratory results were provided by the Division of Clinical Microbiology at the University Hospital of Basel, and the Division of Infection Diagnostics at the Department Biomedicine at the University of Basel, a fully accredited and licensed medical microbiology laboratory according to ISO17025 (SAS219). The women's hospital's ultrasound database system was used to retreive the pathological ultrasound findings that led to serological testing. The main ultrasound findings considered to be associated with congenital infection were noted. Patient records were obtained by the Children's Hospital of Basel in case of confirmed fetal infection with admission to the neonatal unit. For *Borrelia burgdorferi*, CMV, *Toxoplasma gondii*, rubella virus, parvovirus B19, HSV and VZV, IgM and IgG antibodies were tested. When required, additional CMV and toxoplasma IgG avidity testing was performed. Reactive borrelia IgG and/or IgM serology was confirmed by performing line immunoblotting. Detection of HBV surface antigen was used to screen for hepatitis B infection, anti-HCV antibodies for hepatitis C, and a 4th generation test combining the detection of both p24 antigen and anti-HIV-1/2 antibodies was used to screen for HIV. Antibodies of enteroviruses and leptospires were detected by complement-binding reaction. Quantitative polymerase chain reaction (PCR) of amniotic fluid was performed to confirm fetal infection with CMV and parvovirus, and the detection of CMV-DNA in urine was used to confirm CMV infection in a newborn. Maternal CMV infections were diagnosed by seroconversion (case 5), low IgG avidity indices (case 4 and case 7), and increasing IgG avidity indices (from low/medium to high indices) (case 1 and case 6). Two maternal serologies were inconclusive (case 2 and case 3), but fetal infection was confirmed by PCR of amniotic fluid (case 2) and by placental immunohistochemistry (case 3). Maternal parvovirus infections were diagnosed based on the presence of IgM antibodies (case 1, cases 3–6), and based on a positive PCR of amniotic fluid (case 2). Tests for CMV were performed in 344 (87.8%) patients, parvovirus B19 in 316 (80.6%), HSV in 309 (78.8%), *Toxoplasma gondii* in 301 (76.8%), *Borrelia burgdorferi* in 290 (74%), VZV in 286 (73%), HBV in 276 (87.8), *Treponema pallidum* in 270 (68.9%), HCV in 266 (67.9%), rubella virus in 252 (64.3%), HIV in 244 (62.2%), enterovirus in 231 (58.9%), and leptospires in 227 (57.9%) (fig. 1). The study was approved by the ethics committee of north-western and central Switzerland (reference numbers: 2013/142, 2014/143). No informed consent was necessary for the execution of this study.

Results

Indications

In the five-year study period, the number of deliveries was 10,729, of which 392 (3.7%) had STORCH tests per-

Figure 1: Total amount of births during study period, percentage of performed STORCH panels, incidence of maternal and fetal infections.



formed because of abnormal ultrasonographic findings. A detailed list of these findings and the frequency of maternal STORCH infections are shown in table 1. The most common abnormal ultrasound finding leading to STORCH testing was intrauterine growth restriction (IUGR) (30.4%), followed by polyhydramnios (14.8%) and intrauterine fetal death (13.3%). 46% of the ultrasounds showed multiple abnormalities, while in 54% of cases, a STORCH test was performed because of a single suspicious finding. All seven confirmed congenital infections were associated with multiple rather than isolated ultrasonographic abnormalities. Three maternal infections showed a single abnormality (polyhydramnios), and fetal infection was not confirmed in any of these cases. The most common findings associated with maternal infection were hyperechogenic bowel, IUGR, ventricular septum defect (VSD), polyhydramnios and oligohydramnios, prominent cerebral lateral ventricles, fetal hydrops, and cardiomegaly, in descending order. Of the seven confirmed congenital infections, 43% were associated with IUGR, hyperechogenic bowel, and VSD, while 29% were associated with oligohydramnios, prominent lateral ventricles, fetal hydrops, and cardiomegaly. Each of these findings occured in combination with other abnormalities. Microcephaly was reported in 1.5% of cases (table 1).

Maternal infections

There were seven confirmed maternal CMV infections (7/392 = 1.8%), six confirmed maternal parvovirus infections (6/392 = 1.5%), and one of these six patients reported a history of varicella primary infection during early pregnancy in addition to a parvovirus infection (1/392 = 0.3%). Furthermore, there was one suspected case of peripartal enterovirus infection and none of the other infections. Two patients suffered from a chronic hepatitis C infection and one patient from a chronic hepatitis B infection. One woman had been diagnosed with HIV prior to pregnancy. Reactive anti-HSV IgM were observed in 19 patients and reactive anti-borrelia IgM were observed in 31 patients. Follow-up studies revealed no IgG seroconversions and no increases of IgM or IgG. PCRs of amniotic fluid to detect *Borrelia burgdorferi* or HSV were not performed. In conclusion, the reactive IgM results were considered to be polyclonal antibodies occuring in the context of pregnancy. There were no cases of primary syphilis. Seroprevalence rates were 78, 66 and 62% for HSV, parvovirus, and CMV, respectively. Immunisation rates were 94.4 and 98.4% for varicella zoster virus and rubella virus, respectively. Ultrasonographic findings and detailed pregnancy outcomes of confirmed maternal STORCH infections are listed in table 2.

Table 1: Ultrasound indications for maternal STORCH testing.

Finding	Number	Percentage (total 392)	Maternal infections	Percent of indications
IUGR[1]	119	30.4	4	3.4
Polyhydramnios[2]	58	14.8	3	5.2
IUFD	52	13.3	1	1.9
Oligohydramnios	50	12.8	3	6.0
Others[3]	45	11.5	4	8.9
VSD	37	9.4	3	8.1
Increased nuchal translucency[4]	35	8.9	0	0.0
Prominent lateral ventricles	29	7.4	2	6.9
Ventriculomegaly	16	4.1	1	6.3
Macrosomia	14	3.6	0	0.0
Hyperechogenic bowel	13	3.3	4	30.8
Fetal hydrops[5]	13	3.3	2	15.4
Lacunar placenta	11	2.8	0	0.0
Nuchal oedema[6]	11	2.8	1	9.1
Echogenic foci	10	2.6	0	0.0
Bilateral choroid plexus cysts	9	2.3	1	11.1
Prominent cisterna magna	9	2.3	0	0.0
Cardiomegaly	9	2.3	2	22.2
Isolated hydrothorax[7]	8	2.0	0	0.0
Singular umbilical artery	8	2.0	1	12.5
White spot	7	1.8	0	0.0
Isolated pericardial effusion[7]	7	1.8	1	14.3
Isolated ascites[7]	7	1.8	1	14.3
Unilateral choroid plexus cysts	6	1.5	1	16.7
Hydrocephalus	6	1.5	1	16.7
Microcephaly	6	1.5	2	33.3

IUGR = intrauterine growth restriction, IUFD = intrauterine fetal demise, VSD = ventricular septal defect, CNS = central nervous system. [1] IUGR refers to a fetal weight below the 10th percentile for gestational age. [2] Polyhydramnios was defined by the following thresholds: single deepest pocket ≥8 cm or amniotic fluid index (AFI) of ≥24 cm. [3] "Others" included indications that were found in less than 1.5 percent: *Prominent third ventricle (5), placental abnormalities (5), cerebellar hypoplasia (4), ahydramnios (3), dilated bowel (3), agenesis of the corpus callosum (3), generalised skin oedema (3), prominent stomach (2), pleural effusion (2), prominent fourth ventricle (1), prominent bladder (1), prominent renal calices (1), amniotic band constriction (1), lobed choroid plexus (1), choroid plexus haemorrhage (1), multicystic encephalomalacia (1), intrahemispheric CNS cyst (1), intracranial calcifications (1), intracerebral haemorrhage (1), hypoechogenic structure of the CNS (1), hypoplasia of the cerebellar vermis (1), lobed lateral ventricles (1), subependymal pseudocysts (1), and kidney dysplasia (1).* [4] Increased nuchal translucency = between the 95th and 99th percentile. [5] Fetal hydrops was defined by the presence of two or more of the following findings: ascites, pleural effusion, pericardial effusion, polyhydramnios, and skin oedema. [6] Nuchal oedema = over the 99th percentile and over 3.5mm thick. [7] Isolated meaning the occurrence of the finding without two other findings included in the definition of fetal hydrops.

Fetal outcome

Four of the seven maternal CMV infections were transmitted to the fetus (transmission rate 57%). Diagnosis was confirmed either by autopsy (one case), by detection of CMV-DNA in amniotic fluid (two cases), or chorionic villus sampling (one case). Congenital CMV was excluded by testing newborns' urine (one case) or by amniocentesis (one case). It is unclear whether the remaining case of maternal CMV was transmitted to the fetus because testing was not performed. All four confirmed congenital CMV infections displayed multiple ultrasonographic abnormalities. Two of the mothers wished termination of pregnancy after confirmation of congenital infection. Two children had severe symptomatic CMV disease at birth, one of which died on the second day of life. One woman had elevated enterovirus titres at 31 weeks of gestation, when polyhydramnios was seen on ultrasound. No further data concerning diagnostics were found. There were three congenital parvovirus infections (transmission rate 50%). Two of them were confirmed by amniocentesis, and one was likely based on ultrasound findings but was not confirmed by invasive fetal testing. All of the congenital parvovirus infections showed multiple sonographic abnormalities and displayed fetal anemia. Intrauterine transfusions were administered in all three cases. There was one IUFD, in the same woman who had a history of varicella infection in pregnancy. The two other cases of fetal anaemia resolved over the course of pregnancy, but IUGR was severe enough to require premature delivery of one baby.

Discussion

A variety of ultrasonographic findings are associated with fetal infection. Most of these findings are non-specific and can be caused by several other conditions. In our study, a maternal STORCH infection was found in 5.2, 3.4, and 1.9% of the three findings with the largest case numbers, polyhydramnios, IUGR, and IUFD.

Most infections were caused by cytomegalovirus and parvovirus, and all seven confirmed fetal infections displayed multiple sonographic abnormalities. Interestingly, the classic ultrasound findings that are associated with fetal STORCH infections, such as abdominal or intracranial calcifications, were rarely found.

It is believed that congenital infections account for approximately 5–10% of all cases of IUGR [13]. The association of IUGR with congenital infections and the cost-effective-

Table 2: Pregnancy outcomes in cases of confirmed maternal infections.

Case	Ultrasound features	GA at fetal testing	Outcome
Cytomegalovirus			
1	Oligohydramnios, hyperechogenic bowel, IUGR	24 WG (positive AC)	TOP
2	Subependymal pseudocysts, VSD, prominent lateral ventricles	37 WG (positive AC)	Symptomatic infection (cerebral abnormalities, hepatosplenomegaly, hepatopathy, petechiae, coagulopathy, hypoglycemia, thrombocytopenia, direct hyperbilirubinaemia, pathological acoustic emissions
3	Ahydramnios, dysplastic kidneys	Autopsy	Severe generalised CMV infection (petechiae, anaemia, hypoalbuminaemia, thrombocytopenia, lung hypoplasia,cerebral oedema, CMV-myocarditis, renal insufficiency due to CMV nephritis) death 48 hours postpartum
4	Hyperechogenic bowel, ascites, VSD, cerebellar hypoplasia, microcephalus	21 WG (positive CVS)	TOP
5 twins	Nuchal oedema, singular umbilical artery (Fetus 1), bilateral choroid plexus cysts, oligohydramnios (Fetus 2)	17 WG (negative AC)	VB 38+1
6	Polyhydramnios	1st day of life (negative urine PCR)	CS 38+4
7	IUGR, cardiac malformations	Not tested	Symptoms attributable to unclear syndrome (hypoplastic kidneys, bilateral microphthtalmia and microtia, microcephalus) and cardiac malformations (double outlet right ventricle, transposition of the great arteries, dysplastic pulmonary valve)
Parvovirus			
1	Fetal hydrops (ascites, pleural effusion), cardiomegaly, IUGR, prominent left lateral ventricle, increased middle cerebral artery peak systolic velocity	22. WG (positive AC)	VB 38 + 6
2	Fetal hydrops (ascites, generalised skin oedema and hydrothorax), hyperechogenic bowel, VSD, increased middle cerebral arterial peak systolic velocity	20 WG (positive AC)	IUFD 19+4
3	IUGR, oligohydramnios, pericardial effusion, hyperechogenic bowel, cardiomegaly, increased middle cerebral arterial peak systolic velocity	Not tested, but likely	CS 33+1, complications of premature birth (RDS, hyperbilirubinaemia)
4	Ventriculomegaly of lateral ventricles, prominent 3rd ventricle	Not tested	Internal hydrocephalus, hyperbilirubinaemia
5	Choroid plexus cysts, retrochorial hematoma	Not tested	Healthy baby
6	Polyhydramnios	Not tested	Healthy baby
Varizella-zoster virus			
1	Fetal hydrops (ascites, generalised skin oedema and hydrothorax), hyperechogenic bowel, VSD, increased middle cerebral arterial peak systolic velocity	20 WG (negative AC)	IUFD 19+4
Enterovirus			
1	Polyhydramnios	-	No data

GA = gestational age; IUGR = intrauterine growth restriction; WG = weeks of gestation; AC = amniocentesis; TOP = termination of pregnancy; VSD = ventricular septum defect; CVS = chorionic villus sampling; VB = vaginal birth; PCR = polymerase chain reaction; CS = ceasarean section; IUFD = intrauterine fetal demise; RDS = respiratory distress syndrome

ness of STORCH testing in growth-restricted fetuses have been examined by a number of studies. Khan et al. found that the yield of TORCH testing in cases of IUGR (birth weight, height, and/or head circumference <10th%ile for gestational age) is poor and does not justify its costs, as most cases of IUGR in their study were caused by maternal conditions other than infections [10]. Yamamoto et al analysed the systematic screening for *Toxoplasma gondii*, rubella virus, CMV, and HSV among 319 women carrying a fetus with fetal growth restriction and concluded that a complete maternal STORCH test in growth-restricted fetuses appeared unneccessary. The decision to perform a STORCH test should instead be based on ultrasonographic signs and on previous obstetric history [11]. The second most common indication was polyhydramnios. In the absence of maternal signs or symptoms, isolated polyhydramnios is rarely caused by congenital infection [14]. Most causes of polyhydramnios in singleton pregnancies remain idiopathic [15]. In a retrospective study among 860 singleton pregnancies with polyhydramnios, serological evidence of recent STORCH infection was found in 25 women with isolated polyhydramnios (2.9%). The two most common infections were CMV (12 cases) and parvovirus (9 cases). Based on these results, the authors suggested performing a TORCH test following the detection of polyhydramnios [16]. On the other hand, Abdel-Fattah et al. analysed 462 STORCH tests in the UK and out of the 11 confirmed cases of maternal CMV infection, none was associated with polyhydramnios [9]. Fayyaz et al. and Pasquini et al. concluded that STORCH testing is not beneficial in cases of isolated polyhydramnios [14, 17]. The third most common indication was intrauterine fetal demise. Infection accounts for 10 to 25% of all stillbirths in high-income countries [18]. A review of 25 studies found that the prevention and treatment of syphilis and possibly malaria had the clearest evidence of impact in stillbirth reduction [19]. Parvovirus and CMV infection are relatively common and should be considered in stillbirths of unknown etiology after autopsy. Among viral infections leading to stillbirths, parvovirus B19 caused two thirds and CMV one third of all stillbirths [20]. A prospective case-control study that examined the incidence of CMV, parvovirus B19, and HSV-1/2 in intrauterine fetal death showed that CMV-DNA was found in 16% of placentas with IUFD compared to 3% of the control placentas [21]. Iwasenko et al. found CMV-DNA in 15% of examined fetal tissues of 130 singleton stillbirths [22]. Cytomegalovirus is the most common congenital viral infection [23] and is a significant cause of birth defects and developmental disabilities [24–26]. This is contrasted by the limited knowledge pregnant women in Switzerland have about the hazards of CMV infection in pregnancy [27]. In the absence of established maternal treatment that improves perinatal outcome [28, 29], the value of prenatal testing (including invasive fetal testing) is questionable. There is evidence from randomised controlled trials that postnatal treatment with intravenous ganciclocvir or oral valganciclovir prevents hearing deterioration and improves neurodevelopmental outcome in children with symptomatic congenital infections [30–32], but testing could be limited to a urine PCR in the first weeks of life. Maternal treatment with intravenous immunoglobulins (IVIG) was shown to decrease the severity of disabilities caused by fetal CMV infection [33] and was associated with a smaller risk of intrauterine CMV transmission in retrospective studies [34]. However, a randomised trial showed no significant impact on the course of primary CMV infection during pregnancy after the administration of immunoglobulins [29]. A larger randomised trial is currently recruiting patients and results can be expected by May 2018. Treatment with IVIG was offered to all affected women in our study. In the meantime, pregnant women or women trying to get pregnant should be educated about preventive measures [35, 36]. Acute parvovirus infection occurs in about 3.3 to 3.8% of pregnancies with a transmission rate of 25% [37, 38]. Parvovirus is not considered a teratogen, and most congenital infections have a favorable outcome [38, 39]. Typical ultrasound abnormalities are fetal anemia, fetal hydrops, and fetal death due to hydropic changes. Testing could thus be limited to these ultrasound findings, also with regard of available effective treatment in reducing fetal death [40]. Congenital varicella and rubella infections are rather rare. Only about 5% of pregnant women in Europe are susceptible to VZV infection during pregnancy [41, 42], and varicella embryopathy occurs in approximately 2% of maternal primary infections before 20 weeks of gestation [43]. The incidence of rubella infections has been monitored by the Swiss paediatric surveillance unit (SPSU) since 1995. Until 2012, three cases of congenital rubella syndrome, one congenital rubella infection and six rubella infections during pregnancy have been reported [44]. Leptospirosis is known to cause spontaneous abortion in animals, and cases of spontaneous abortions in humans due to leptospirosis in pregnancy have been reported [45]. However, the rate of fetal transmission is unknown and there is a lack of information about the outcome of surviving neonates [46]. Although rare cases of intrauterine fetal death due to enterovirus infection have been reported [47], it does not readily cross the placenta or cause fetal disease [48], and vertical transmission most likely occurs in the perinatal period [49]. Maternal infection is not thought to cause congenital damage, although congenital anormalities have been reported [50, 51]. In conclusion, STORCH testing based on abnormal ultrasonography could be limited to the two most common infections, CMV and parvovirus, considering (1) the presence of multiple rather than isolated ultrasonographic abnormalities, (2) a history of symptoms and/or exposure, and (3) results of previous serologies. The incidence of STORCH infections in our sample probably underestimates the real incidence. First, our sample is not representative of all pregnant patients with abnormal ultrasound findings. As we lack data concerning the number of abnormal ultrasounds and only included abnormal ultrasounds that were followed by a STORCH serology, we cannot make a statement about the percentage of all abnormal ultrasounds that were possibly caused by fetal infection. Second, not all fetal infections displayed abnormal ultrasound findings. It it therefore very likely that there were some fetal infections that were never detected prenatally because there were no ultrasound abnormalities and therefore no indications to perform a STORCH test. It is important to be aware of the limitations of ultrasound, as most abnormalities are not specific and can occur in the absence of underlying disease [52–54]. A retrospective cohort study found that among 154 fetuses with congenital CMV infections, only 14.9%

showed abnormal ultrasonographic findings [55]. Most importantly, normal ultrasonography of infected fetuses does not exclude symptomatic disease or manifestations in later life [56–60]. Third, serology results might be misleading depending on the timing of the sample and require careful interpretation. Negative CMV IgM and high CMV IgG avidity indices during late pregnancy do not exclude early intrauterine transmission caused by periconceptional primary infection or CMV reactivation. The latency for the development of ultrasound abnormalities is accompanied by the disappearance of IgM and the maturation from low- to high-avidity IgG indexes in CMV infection. Similarly, by the time fetal hydrops due to parvovirus infection becomes apparent, maternal IgM might have already dropped below the limit of detection [61].

STORCH infections remain an important cause of congenitally acquired disease and the recent outbreak of the zika virus gives this topic new relevance [62]. A few imported cases of zika infections have already been reported in Switzerland [63]. Although the risk of a local epidemic is low, the possibility of sexual transmission in addition to acquiring the infection in epidemic regions makes the spread of the virus to pregnant women an important concern [64]. Further studies concerncing the cost-effectiveness of STORCH testing for specific ultrasound findings are needed. However, in the light of the results reported by us and others, and the success of screening pregnant women for HIV infection and syphilis in preventing mother-to- child transmission, our study raises the questions about optimal testing for the risk of CMV and parvovirus B19 testing. Clearly, studies with higher case numbers are needed to determine the value of specific combinations in predicting the probability of fetal infection.

Disclosure statement

No financial support and no other potential conflict of interest relevant to this article was reported.

References

1 Nahmias AJ, Walls KW, Stewart JA, Herrmann KL, Flynt WJ. The ToRCH complex-perinatal infections associated with toxoplasma and rubella, cytomegol- and herpes simplex viruses. Pediatr Res. 1971;5(8):405–6. doi: http://dx.doi.org/10.1203/00006450-197108000-00144.

2 Kinney JS, Kumar ML. Should we expand the TORCH complex? A description of clinical and diagnostic aspects of selected old and new agents. Clin Perinatol. 1988;15(4):727–44. PubMed.

3 Coyne CB, Lazear HM. Zika virus - reigniting the TORCH. Nat Rev Microbiol. 2016;14(11):707–15. doi: http://dx.doi.org/10.1038/nrmicro.2016.125. PubMed.

4 Johansson MA, Mier-y-Teran-Romero L, Reefhuis J, Gilboa SM, Hills SL. Zika and the Risk of Microcephaly. N Engl J Med. 2016;375(1):1–4. doi: http://dx.doi.org/10.1056/NEJMp1605367. PubMed.

5 Petersen EE, Staples JE, Meaney-Delman D, Fischer M, Ellington SR, Callaghan WM, et al. Interim Guidelines for Pregnant Women During a Zika Virus Outbreak--United States, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(2):30–3. doi: http://dx.doi.org/10.15585/mmwr.mm6502e1. PubMed.

6 Demmler GJ. Infectious Diseases Society of America and Centers for Disease Control. Summary of a workshop on surveillance for congenital cytomegalovirus disease. Rev Infect Dis. 1991;13(2):315–29. doi: http://dx.doi.org/10.1093/clinids/13.2.315. PubMed.

7 Stagno S, Pass RF, Alford CA. Perinatal infections and maldevelopment. Birth Defects Orig Artic Ser. 1981;17(1):31–50. PubMed.

8 Canfield MA, Honein MA, Yuskiv N, Xing J, Mai CT, Collins JS, et al. National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999-2001. Birth Defects Res A Clin Mol Teratol. 2006;76(11):747–56. doi: http://dx.doi.org/10.1002/bdra.20294. PubMed.

9 Abdel-Fattah SA, Bhat A, Illanes S, Bartha JL, Carrington D. TORCH test for fetal medicine indications: only CMV is necessary in the United Kingdom. Prenat Diagn. 2005;25(11):1028–31. doi: http://dx.doi.org/10.1002/pd.1242. PubMed.

10 Khan NA, Kazzi SN. Yield and costs of screening growth-retarded infants for torch infections. Am J Perinatol. 2000;17(3):131–5. doi: http://dx.doi.org/10.1055/s-2000-9288. PubMed.

11 Yamamoto R, Ishii K, Shimada M, Hayashi S, Hidaka N, Nakayama M, et al. Significance of maternal screening for toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus infection in cases of fetal growth restriction. J Obstet Gynaecol Res. 2013;39(3):653–7. doi: http://dx.doi.org/10.1111/j.1447-0756.2012.02012.x. PubMed.

12 Boubaker K, et al. Verzicht auf das Toxoplasmose-Screening in der Schwangerschaft. Swiss Med Forum. 2009:9(5):105–6.

13 Knox GE. Influence of infection on fetal growth and development. J Reprod Med. 1978;21(6):352–8. PubMed.

14 Fayyaz H, Rafi J. TORCH screening in polyhydramnios: an observational study. J Matern Fetal Neonatal Med. 2012;25(7):1069–72. doi: http://dx.doi.org/10.3109/14767058.2011.622002. PubMed.

15 Abele H, Starz S, Hoopmann M, Yazdi B, Rall K, Kagan KO. Idiopathic polyhydramnios and postnatal abnormalities. Fetal Diagn Ther. 2012;32(4):251–5. doi: http://dx.doi.org/10.1159/000338659. PubMed.

16 Kollmann M, Voetsch J, Koidl C, Schest E, Haeusler M, Lang U, et al. Etiology and perinatal outcome of polyhydramnios. Ultraschall Med. 2014;35(4):350–6. doi: http://dx.doi.org/10.1055/s-0034-1366115. PubMed.

17 Pasquini L, Seravalli V, Sisti G, Battaglini C, Nepi F, Pelagalli R, et al. Prevalence of a positive TORCH and parvovirus B19 screening in pregnancies complicated by polyhydramnios. Prenat Diagn. 2016;36(3):290–3. doi: http://dx.doi.org/10.1002/pd.4769. PubMed.

18 Goldenberg RL, McClure EM, Saleem S, Reddy UM. Infection-related stillbirths. Lancet. 2010;375(9724):1482–90. doi: http://dx.doi.org/10.1016/S0140-6736(09)61712-8. PubMed.

19 Ishaque S, Yakoob MY, Imdad A, Goldenberg RL, Eisele TP, Bhutta ZA. Effectiveness of interventions to screen and manage infections during pregnancy on reducing stillbirths: a review. BMC Public Health. 2011;11(Suppl 3):S3. doi: http://dx.doi.org/10.1186/1471-2458-11-S3-S3. PubMed.

20 Williams EJ, Embleton ND, Clark JE, Bythell M, Ward Platt MP, Berrington JE. Viral infections: contributions to late fetal death, stillbirth, and infant death. J Pediatr. 2013;163(2):424–8. doi: http://dx.doi.org/10.1016/j.jpeds.2013.02.004. PubMed.

21 Syridou G, Spanakis N, Konstantinidou A, Piperaki ET, Kafetzis D, Patsouris E, et al. Detection of cytomegalovirus, parvovirus B19 and herpes simplex viruses in cases of intrauterine fetal death: association with pathological findings. J Med Virol. 2008;80(10):1776–82. doi: http://dx.doi.org/10.1002/jmv.21293. PubMed.

22 Iwasenko JM, Howard J, Arbuckle S, Graf N, Hall B, Craig ME, et al. Human cytomegalovirus infection is detected frequently in stillbirths and is associated with fetal thrombotic vasculopathy. J Infect Dis. 2011;203(11):1526–33. doi: http://dx.doi.org/10.1093/infdis/jir121. PubMed.

23 Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol. 2007;17(4):253–76. doi: http://dx.doi.org/10.1002/rmv.535. PubMed.

24 Cannon MJ, Davis KF. Washing our hands of the congenital cytomegalovirus disease epidemic. BMC Public Health. 2005;5(1):70. doi: http://dx.doi.org/10.1186/1471-2458-5-70. PubMed.

25 Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol. 2007;17(5):355–63. doi: http://dx.doi.org/10.1002/rmv.544. PubMed.

26 Grosse SD, Ross DS, Dollard SC. Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: a quantitative assessment. J Clin Virol. 2008;41(2):57–62. doi: http://dx.doi.org/10.1016/j.jcv.2007.09.004. PubMed.

27 Willame A, Blanchard-Rohner G, Combescure C, Irion O, Posfay-Barbe K, Martinez de Tejada B. Awareness of Cytomegalovirus Infection among Pregnant Women in Geneva, Switzerland: A Cross-sectional Study. Int J Environ Res Public Health. 2015;12(12):15285–97. doi: http://dx.doi.org/10.3390/ijerph121214982. PubMed.

28 Jacquemard F, Yamamoto M, Costa JM, Romand S, Jaqz-Aigrain E, Dejean A, et al. Maternal administration of valaciclovir in symptomatic intrauterine cytomegalovirus infection. BJOG. 2007;114(9):1113–21. doi: http://dx.doi.org/10.1111/j.1471-0528.2007.01308.x. PubMed.

29 Revello MG, Lazzarotto T, Guerra B, Spinillo A, Ferrazzi E, Kustermann A, et al.; CHIP Study Group. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. N Engl J Med.

2014;370(14):1316–26. doi: http://dx.doi.org/10.1056/NEJMoa1310214. PubMed.
30 Oliver SE, Cloud GA, Sánchez PJ, Demmler GJ, Dankner W, Shelton M, et al.; National Institute of Allergy, Infectious Diseases Collaborative Antiviral Study Group. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. J Clin Virol. 2009;46(Suppl 4):S22–6. doi: http://dx.doi.org/10.1016/j.jcv.2009.08.012. PubMed.
31 Kimberlin DW, Lin CY, Sánchez PJ, Demmler GJ, Dankner W, Shelton M, et al.; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. J Pediatr. 2003;143(1):16–25. doi: http://dx.doi.org/10.1016/S0022-3476(03)00192-6. PubMed.
32 Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al.; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med. 2015;372(10):933–43. doi: http://dx.doi.org/10.1056/NEJMoa1404599. PubMed.
33 Nigro G, Adler SP, Parruti G, Anceschi MM, Coclite E, Pezone I, et al. Immunoglobulin therapy of fetal cytomegalovirus infection occurring in the first half of pregnancy--a case-control study of the outcome in children. J Infect Dis. 2012;205(2):215–27. doi: http://dx.doi.org/10.1093/infdis/jir718. PubMed.
34 Buxmann H, Stackelberg OM, Schlößer RL, Enders G, Gonser M, Meyer-Wittkopf M, et al. Use of cytomegalovirus hyperimmunoglobulin for prevention of congenital cytomegalovirus disease: a retrospective analysis. J Perinat Med. 2012;40(4):439–46. doi: http://dx.doi.org/10.1515/jpm-2011-0257. PubMed.
35 Vauloup-Fellous C, Picone O, Cordier AG, Parent-du-Châtelet I, Senat MV, Frydman R, et al. Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital. J Clin Virol. 2009;46(Suppl 4):S49–53. doi: http://dx.doi.org/10.1016/j.jcv.2009.09.003. PubMed.
36 Revello MG, Tibaldi C, Masuelli G, Frisina V, Sacchi A, Furione M, et al.; CCPE Study Group. Prevention of Primary Cytomegalovirus Infection in Pregnancy. EBioMedicine. 2015;2(9):1205–10. doi: http://dx.doi.org/10.1016/j.ebiom.2015.08.003. PubMed.
37 Rodis JF, Quinn DL, Gary GW, Jr, Anderson LJ, Rosengren S, Cartter ML, et al. Management and outcomes of pregnancies complicated by human B19 parvovirus infection: a prospective study. Am J Obstet Gynecol. 1990;163(4 Pt 1):1168–71. doi: http://dx.doi.org/10.1016/0002-9378(90)90681-V. PubMed.
38 Gratacós E, Torres PJ, Vidal J, Antolín E, Costa J, Jiménez de Anta MT, et al. The incidence of human parvovirus B19 infection during pregnancy and its impact on perinatal outcome. J Infect Dis. 1995;171(5):1360–3. doi: http://dx.doi.org/10.1093/infdis/171.5.1360. PubMed.
39 Ergaz Z, Ornoy A. Parvovirus B19 in pregnancy. Reprod Toxicol. 2006;21(4):421–35. doi: http://dx.doi.org/10.1016/j.reprotox.2005.01.006. PubMed.
40 von Kaisenberg CS, Jonat W. Fetal parvovirus B19 infection. Ultrasound Obstet Gynecol. 2001;18(3):280–8. doi: http://dx.doi.org/10.1046/j.1469-0705.2001.00471.x. PubMed.
41 Alanen A, Kahala K, Vahlberg T, Koskela P, Vainionpää R. Seroprevalence, incidence of prenatal infections and reliability of maternal history of varicella zoster virus, cytomegalovirus, herpes simplex virus and parvovirus B19 infection in South-Western Finland. BJOG. 2005;112(1):50–6. doi: http://dx.doi.org/10.1111/j.1471-0528.2004.00320.x. PubMed.
42 Plans P, Costa J, Espuñes J, Plasència A, Salleras L. Prevalence of varicella-zoster antibodies in pregnant women in Catalonia (Spain). Rationale for varicella vaccination of women of childbearing age. BJOG. 2007;114(9):1122–7. doi: http://dx.doi.org/10.1111/j.1471-0528.2007.01454.x. PubMed.
43 Pastuszak AL, Levy M, Schick B, Zuber C, Feldkamp M, Gladstone J, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. N Engl J Med. 1994;330(13):901–5. doi: http://dx.doi.org/10.1056/NEJM199403313301305. PubMed.
44 Rudi C, Bernet V, Posfay Barbe K, Laubscher B, Simonetti G, Mäusezahl M, et al. SPSU-Jahresbericht. 2013;2014(38):615–27.
45 Shaked Y, Shpilberg O, Samra D, Samra Y. Leptospirosis in pregnancy and its effect on the fetus: case report and review. Clin Infect Dis. 1993;17(2):241–3. doi: http://dx.doi.org/10.1093/clinids/17.2.241. PubMed.
46 Carles G, Montoya E, Joly F, Peneau C. [Leptospirosis and pregnancy. Eleven cases in French Guyana]. J Gynecol Obstet Biol Reprod (Paris). 1995;24(4):418–21. PubMed.
47 Johansson ME, Holmström S, Abebe A, Jacobsson B, Ekman G, Samuelson A, et al. Intrauterine fetal death due to echovirus 11. Scand J Infect Dis. 1992;24(3):381–5. doi: http://dx.doi.org/10.3109/00365549209061347. PubMed.
48 Amstey MS, Miller RK, Menegus MA, di Sant 'Agnese PA. Enterovirus in pregnant women and the perfused placenta. Am J Obstet Gynecol. 1988;158(4):775–82. doi: http://dx.doi.org/10.1016/0002-9378(88)90071-3. PubMed.
49 Modlin JF. Perinatal echovirus infection: insights from a literature review of 61 cases of serious infection and 16 outbreaks in nurseries. Rev Infect Dis. 1986;8(6):918–26. doi: http://dx.doi.org/10.1093/clinids/8.6.918. PubMed.
50 Elizan TS, Ajero-Froehlich L, Fabiyi A, Ley A, Sever JL. Viral infection in pregnancy and congenital CNS malformations in man. Arch Neurol. 1969;20(2):115–9. doi: http://dx.doi.org/10.1001/archneur.1969.00480080015001. PubMed.
51 Gauntt CJ, Gudvangen RJ, Brans YW, Marlin AE. Coxsackievirus group B antibodies in the ventricular fluid of infants with severe anatomic defects in the central nervous system. Pediatrics. 1985;76(1):64–8. PubMed.
52 Koopman E, Wladimiroff JW. Fetal intrahepatic hyperechogenic foci: prenatal ultrasound diagnosis and outcome. Prenat Diagn. 1998;18(4):339–42. doi: http://dx.doi.org/10.1002/(SICI)1097-0223(199804)18:4<339::AID-PD265>3.0.CO;2-8. PubMed.
53 Petrikovsky BM, Challenger M, Wyse LJ. Natural history of echogenic foci within ventricles of the fetal heart. Ultrasound Obstet Gynecol. 1995;5(2):92–4. doi: http://dx.doi.org/10.1046/j.1469-0705.1995.05020092.x. PubMed.
54 Ji EK, Lee EK, Kwon TH. Isolated echogenic foci in the left upper quadrant of the fetal abdomen: are they significant? J Ultrasound Med. 2004;23(4):483–8. doi: http://dx.doi.org/10.7863/jum.2004.23.4.483. PubMed.
55 Guerra B, Simonazzi G, Puccetti C, Lanari M, Farina A, Lazzarotto T, et al. Ultrasound prediction of symptomatic congenital cytomegalovirus infection. Am J Obstet Gynecol. 2008;198(4):380.e1–7. doi: http://dx.doi.org/10.1016/j.ajog.2007.09.052. PubMed.
56 Guerra B, Lazzarotto T, Quarta S, Lanari M, Bovicelli L, Nicolosi A, et al. Prenatal diagnosis of symptomatic congenital cytomegalovirus infection. Am J Obstet Gynecol. 2000;183(2):476–82. doi: http://dx.doi.org/10.1067/mob.2000.106347. PubMed.
57 Liesnard C, Donner C, Brancart F, Gosselin F, Delforge ML, Rodesch F. Prenatal diagnosis of congenital cytomegalovirus infection: prospective study of 237 pregnancies at risk. Obstet Gynecol. 2000;95(6 Pt 1):881–8. PubMed.
58 Lipitz S, Achiron R, Zalel Y, Mendelson E, Tepperberg M, Gamzu R. Outcome of pregnancies with vertical transmission of primary cytomegalovirus infection. Obstet Gynecol. 2002;100(3):428–33. PubMed.
59 Lipitz S, Hoffmann C, Feldman B, Tepperberg-Dikawa M, Schiff E, Weisz B. Value of prenatal ultrasound and magnetic resonance imaging in assessment of congenital primary cytomegalovirus infection. Ultrasound Obstet Gynecol. 2010;36(6):709–17. doi: http://dx.doi.org/10.1002/uog.7657. PubMed.
60 Enders G, Bäder U, Lindemann L, Schalasta G, Daiminger A. Prenatal diagnosis of congenital cytomegalovirus infection in 189 pregnancies with known outcome. Prenat Diagn. 2001;21(5):362–77. doi: http://dx.doi.org/10.1002/pd.59. PubMed.
61 Enders M, Weidner A, Rosenthal T, Baisch C, Hedman L, Söderlund-Venermo M, et al. Improved diagnosis of gestational parvovirus B19 infection at the time of nonimmune fetal hydrops. J Infect Dis. 2008;197(1):58–62. doi: http://dx.doi.org/10.1086/524302. PubMed.
62 Bahlmann AS, Theilacker C, Hirsch H. Update Zikavirus. Swiss Med Forum, 2016;16:600–04.
63 Gesundheit Br. Verbreitung des Zika-Virus: Situation und Empfehlungen. Bulletin. 2016;30:465–9.
64 Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerg Infect Dis. 2015;21(2):359–61. doi: http://dx.doi.org/10.3201/eid2102.141363. PubMed.