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SYSTEMATIC REVIEW

Maternal infection with Zika virus and prevalence of congenital disorders in infants: systematic review and meta-analysis

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Abstract

Objective Zika virus (ZIKV) infection is a vector-borne disease that can be transmitted sexually and vertically. The vertical transmission of the virus may lead to congenital Zika syndrome in infants. The aim of this study is to conduct a systematic review and meta-analysis of published reports documenting the prevalence of congenital Zika-related disorders in infants of mothers infected with ZIKV during pregnancy.

Methods We conducted a comprehensive search in Ovid MEDLINE, Ovid MEDLINE (R) Epub ahead of print, Embase, Embase Classic and Web of Science databases to identify human studies reporting prevalence of congenital disorders in infants of ZIKV-infected mothers.

Results We identified 25 reports selected for inclusion in the current study ($n = 4683$ subjects). The majority of the studies were from South American high-risk countries. Only one third of the identified studies were conducted in the United States. Clinical maternal symptoms included maculopapular rash (76.9%), arthralgia (46.4%), fever (45.5%) and headache (31.8%) with myalgia and conjunctivitis only presented in 25% of the cases. The most prevalent congenital disorder in the newborns was brain calcifications (42.6; 95% CI, 30.8–54.4), followed by ventriculomegaly (21.8; 95% CI, 15.2–28.4), joint abnormalities (13.2; 95% CI, 9.4–18.2), ocular abnormalities (4.2; 95% CI, 1.0–7.5) and microcephaly (3.9; 95% CI, 2.4–5.4).

Conclusion The current study highlights the high prevalence of a range of congenital disorders in newborns of mothers infected with ZIKV. It warrants developing studies to further clarify the mechanisms by which each of these disorders occurs in response to the viral infection during pregnancy and its vertical transmission to the infants.

Résumé

Objectif L'infection par le virus Zika (ZIKV) est une maladie à vecteur pouvant être transmise sexuellement et verticalement. La transmission verticale du virus peut entraîner un syndrome congénital de Zika chez les nourrissons. Le but de cette étude est de réaliser une revue systématique et une méta-analyse de rapports publiés documentant la prévalence de troubles congénitaux liés au Zika chez les nourrissons de mères infectées par le ZIKV pendant la grossesse.

Méthodes Nous avons effectué une recherche exhaustive dans les bases de données Ovid MEDLINE, Ovid MEDLINE (R) avant impression, Embase, Embase Classic et Web of Science afin d'identifier des études humaines rapportant la prévalence de troubles congénitaux chez les nourrissons de mères infectées par le ZIKV.

Résultats Nous avons identifié 25 rapports sélectionnés pour inclusion dans la présente étude ($n = 4\,683$ sujets). La majorité des études ont été réalisées dans des pays d'Amérique du Sud présentant un risque élevé. Seulement un tiers des études identifiées ont été menées aux États-Unis. Les symptômes maternels cliniques incluaient une éruption maculo-papuleuse (76,9 %), une arthralgie (46,4 %), une fièvre (45,5 %) et des maux de tête (31,8 %) avec myalgie et conjonctivite ne se présentant que dans

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25 % des cas. Les troubles congénitaux les plus fréquents chez les nouveau-nés étaient les calcifications cérébrales (42,6, IC à 95% : 30,8–54,4), suivies par la ventriculomégalie (21,8, IC à 95% : 15,2–28,4), les anomalies articulaires (13,2, IC à 95% : 9,4–18,2), des anomalies oculaires (4,2, IC à 95% : 1,0–7,5) et une microcéphalie (3,9, IC à 95% : 2,4–5,4).

Conclusion La présente étude met en évidence la prévalence élevée d'une gamme de troubles congénitaux chez les nouveau-nés de mères infectées par le ZIKV. Cela justifie de développer des études pour préciser davantage les mécanismes par lesquels chacun de ces troubles se produit en réponse à l'infection virale pendant la grossesse et à sa transmission verticale aux nourrissons.

Keywords Zika virus · Microcephaly · Congenital disease · Brain calcification · Systematic review

Mots-clés Virus Zika · Microcéphalie · Maladie congénitale · Calcification du cerveau · Revue systématique

Introduction

Zika virus (ZIKV) is an arbovirus belonging to the *flaviviridae* family, as dengue, West Nile and chikungunya viruses, and is transmitted by arthropod vectors, mainly *Aedes* genus (e.g., *Ae. aegypti*) and can also spread through bodily fluid contact, blood transfusions, sexual transmission and vertical transmission (Wikan and Smith 2016). In 2007, Zika virus caused an outbreak on the island of Yap, Micronesia affecting ~ 75% of the local population (Wikan and Smith 2016). Following the suspected transmission from French Polynesia, autochthonous cases of ZIKV were identified in Brazil in May 2015 to spread to over 80 countries or territories across the globe (Wikan and Smith 2016; Brasil et al. 2016).

Identifying a patient with ZIKV infection can be challenging as the virus is asymptomatic in many cases. In symptomatic cases, infection may cause symptoms such as fever, lymphadenopathy and a number of Zika-specific symptoms such as maculopapular rash, and conjunctival injection (Brasil et al. 2016). Still, these symptoms may not be specific to ZIKV infection—one of the main obstacles to detecting the disease appropriately. Of the most alarming consequences is the ability of the virus to attack neuronal cells and cause neurological disorders in both developed and developing neurons (Hu et al. 2017). This may lead to severe consequences, particularly in uterus development. Vertical transmission of the virus with potential to cause neurological defects in fetuses was evident when ZIKV RNA was detected in the placenta, amniotic fluid and even fetal tissue (Noronha Ld et al. 2016).

A study reporting the prevalence of microcephaly in ZIKV-infected regions of Brazil (Kleber de Oliveira et al. 2016) reported a significant increase in the incidence of microcephaly immediately subsequent to the emergence of the virus in many areas where infected pregnant women were identified. In addition to severe microcephaly, there is an array of other congenital ZIKV-associated disorders that were reported in the fetuses of infected pregnant women and are unique to congenital ZIKV infection (Moore et al. 2017). These include cerebral cortices with subcortical calcifications, macular scarring and focal pigmentary retinal mottling, early hypertonia and symptoms of extrapyramidal involvement (Moore et al. 2017). Such widespread irreversible development disorders in newborns and the breadth of the ZIKV global spread, together with the related implications on healthcare, economy and overall well-being, all have led the World Health Organization to declare the ZIKV infection in February 2016 as a public health emergency of concern (Gulland 2016).

The current study was undertaken to conduct a systematic review and meta-analysis of published literature to describe the prevalence of a range of congenital diseases most associated with ZIKV infection. This will permit exploring the possible contribution of the infection in the burden of congenital disorders in infants and may facilitate developing public health measures and actions to curb their incidence.

Methods

Literature search

A systematic review in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) framework (Supplementary Table 1, Fig. 1) was carried out (Liberati et al. 2009). The literature search was conducted in Ovid MEDLINE, Ovid MEDLINE (R) Epub Ahead of Print, Embase and Embase Classic using the search terms (MeSH): "Zika" and/or "ZIKV" AND the congenital disease of interest combined with OR (Supplementary Tables 2 and 3). The time period of the search was from the inception of the databases to the end of October 2017. Only English-language articles on human subjects were included. Review papers, letters to the editor, vaccine trials, case reports, animal studies, conference abstracts and duplicated studies were excluded. Studies were only included if they contained primary data on the prevalence of any congenital disorder of interest in infants of pregnant women infected with Zika virus. Also, we conducted a similar search in the "Latin American and Caribbean Center on Health Science Information"—LILACs, using the same search terms and time period. We identified 34 English-language articles, of which 31 papers were not relevant to the study objective or fell within our

exclusion criteria. Only two reports were relevant to this study: evaluating the frequencies of epileptic seizures (Alves et al. 2016) and ophthalmological findings (Ventura et al. 2016). Since these were the only reports on such conditions, there was not enough information to include either in our meta-analysis.

Inter-reviewer agreement

Two reviewers (SFN and SGR) independently reviewed the abstracts yielded from the search to determine those eligible for full-article review and inclusion in the study. Disagreements regarding study inclusion were resolved by an arbitrator (AB). Percentage agreement and Cohen's Kappa (κ) score were calculated (Alves et al. 2016) and interpreted as described before (Badawi et al. 2018). The agreement between the two reviewers was excellent with a κ of 0.89 (95% CI, 0.82–0.97) (Ventura et al. 2016).

Data extraction and analysis

Data extracted from the selected studies included author's name, year of publication, country of study, dates of patient recruitment, study population and the frequency of maternal symptoms such as rash, fever, conjunctivitis, arthralgia, headache and myalgia (%). The primary outcome measure of the current study was the prevalence of congenital disorders in infants (%) and data were extracted for conditions such as microcephaly, hydranencephaly, calcifications, ventriculomegaly, craniofacial disproportion, brainstem dysfunction, holoprosencephaly, craniosynostosis, encephalocele, meningoencephalitis, paraplegia, Blake's pouch cyst, dyspnea, dysphagia, cerebral hyperechogenicity, and abnormalities in the cortices, corpus callosum, pons, optic nerve, cataracts, ears, joints and/or muscles. Of these conditions, only microcephaly, ventriculomegaly, brain calcification and ocular and joint abnormalities were the congenital disorders reported in at least three of the selected studies and were further evaluated for their prevalence. Meta-analysis of proportions (and 95% CI) was calculated for the clinical maternal symptoms and for a range of the selected congenital disorders—where sufficient set of data was available from the selected studies—using OpenMeta Analyst version 10.10, a free, cross-platform, open-source program (Wallace et al. 2012). We used binary random effects model as described before (Badawi et al. 2018), assuming that the proportion of the congenital diseases in infants of ZIKV-infected mothers is varied across populations. To assess whether there is true heterogeneity among the selected studies and that all the studies are evaluating the same effect within the same congenital diseases, we used the Q test that informs about the presence versus the absence of heterogeneity but does not report on the extent of such heterogeneity. Therefore, we calculated the I^2 index (%) to complement the Q test and quantify the degree of heterogeneity among studies (Higgins and Thompson 2002). Given the limited power of Q test to detect true heterogeneity among a small number of studies, we also quantified the true heterogeneity by estimating the between-study variance in the random effects model (τ^2), as previously described (DerSimonian and Laird 1986). $P < 0.05$ was considered to be statistically significant. Forest plots were used to illustrate the prevalence of a range of congenital diseases in infants of ZIKV-infected mothers from the selected studies and to inspect the heterogeneity of the individual findings. Publication bias was evaluated by regression test (Egger's test) for Funnel plot asymmetry (Supplementary Table 4). Egger's test assesses the tendency for the effects estimated from small sample size studies to differ from those estimated in larger studies.

Results

Search results

In the current study, the initial database and bibliography search yielded 1592 records which met the search inclusion/exclusion criteria (Supplementary Table 2). Following the removal of duplicate studies, 1492 records were screened for abstract review. Of those, 211 abstracts were eligible for full-text review. Based on the inclusion/exclusion criteria, 186 full-text articles were excluded (Fig. 1). Briefly, 46 did not report on the frequency of congenital disorders, 38 had the entire study population with congenital disorders, 33 were case reports/series with less than 3 cases, 24 were reviews, 4 were on an adult/paediatric population, 4 were letters, 3 had data pooled from literature, 2 were commentaries, 2 were non-English studies and 1 was an intervention study. In total, 25 studies examining the prevalence of congenital disorders of infants born to ZIKV-infected mothers were selected for inclusion in the current review (Table 1) (Brasil et al. 2016; Adhikari et al. 2017; Adams et al. 2016; Aragao et al. 2017; Besnard et al. 2016; Bhatnagar et al. 2017; Gregianini et al. 2017; Guillemette-Artur et al. 2016; Hall et al. 2017; Hamer et al. 2017; Honein et al. 2017; Kam et al. 2017; Meaney-Delman et al. 2016; Meaney-Delman et al. 2016; Millet et al. 2017; Rao et al. 2017; Reagan-Steiner et al. 2017; Reynolds et al. 2017; Schaub et al. 2017; Soares de Oliveira-Szejnfeld et al. 2016; Sohan and Cyrus 2017; Zambrano et al. 2017; Zin et al. 2017; Pacheco et al. 2016; Pomar et al. 2017).

Prevalence of congenital disorders

Systematic analysis of the selected studies reporting on the prevalence of the congenital diseases of interest had a total of 4683 mothers infected with the ZIKV during pregnancy. The majority of the studies were in South American countries,

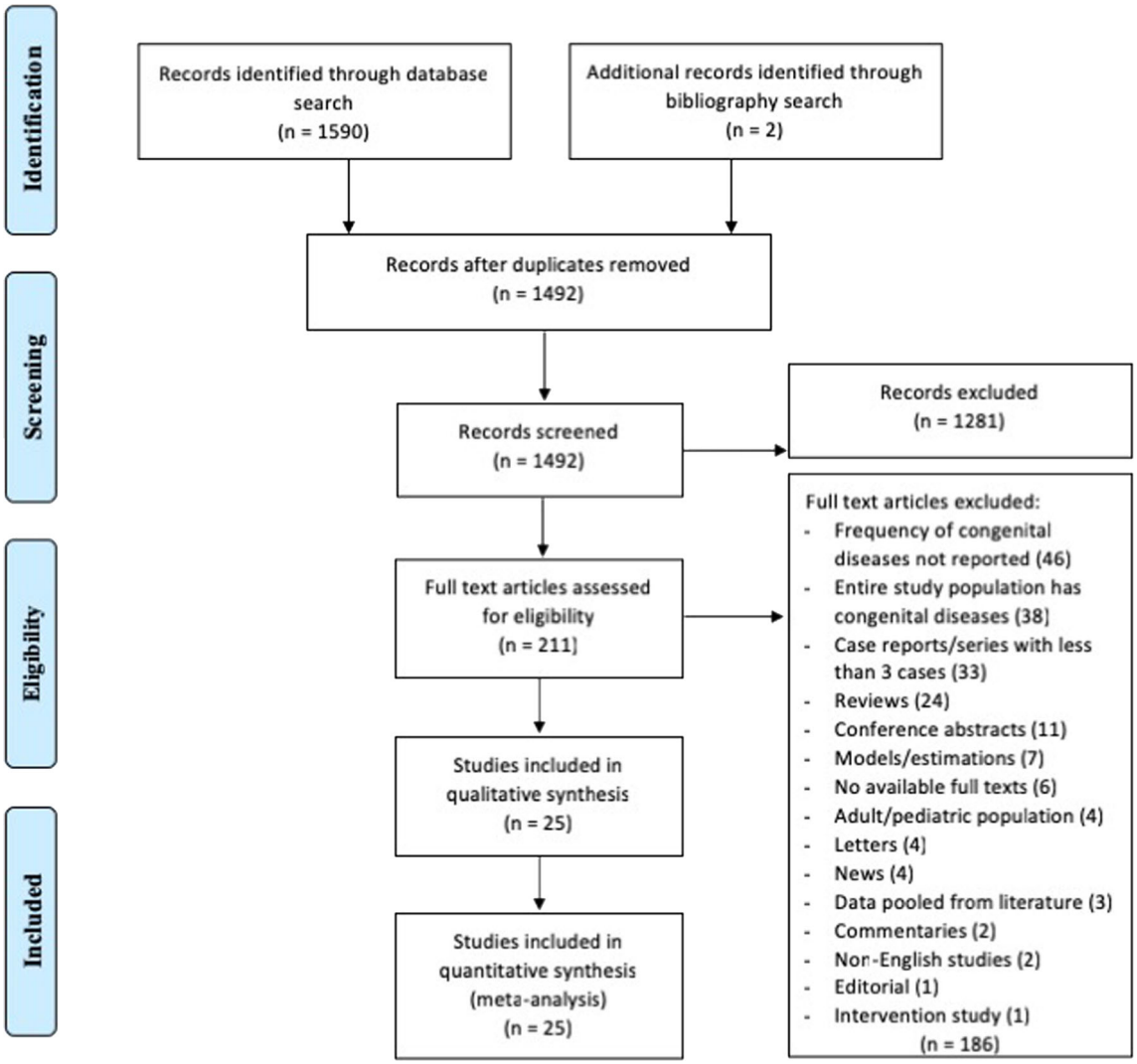


Fig. 1 Flowchart of study selection and systematic literature review process. The flow diagram describes the systematic review of literature evaluating the prevalence of congenital disorders in infants of mothers infected with the Zika virus during pregnancy. Full texts of 211 studies were examined and 25 unique reports were identified to be included in the quantitative assessment and analysis

including Brazil (Brasil et al. 2016; Aragao et al. 2017; Gregianini et al. 2017; Kam et al. 2017; Soares de Oliveira-Szejnfeld et al. 2016; Zin et al. 2017), Colombia (Bhatnagar et al. 2017; Pacheco et al. 2016), Puerto Rico (Adams et al. 2016), French Polynesia (Guillemette-Artur et al. 2016), Martinique (Schaub et al. 2017), Trinidad and Tobago (Sohan and Cyrus 2017), French Guiana (Pomar et al. 2017) and Ecuador (Zambrano et al. 2017) (Table 1). Eight studies were conducted in the US and tended to focus on women who had recently travelled to South American or other Zika-infected countries (Adhikari et al. 2017; Hall et al. 2017; Honein et al. 2017; Meaney-Delman et al. 2016; Meaney-Delman et al. 2016; Rao et al. 2017; Reagan-Steiner et al. 2017; Reynolds et al. 2017). One study was conducted in Spain (Millet et al. 2017). The number of cases in the selected studies varied by approximately 371-fold as it ranged from 4 to 1484 cases. As shown in Table 2, the most prevalent clinical symptom (%) in mothers infected with ZIKV was maculopapular rash (76.9; 95% CI, 48.5–105.3), followed by arthralgia (46.4; 95% CI, 32.9–60.0), fever (45.5; 95% CI, 23.4–67.7) and headache (31.8; 95% CI, 10.9–52.6). Myalgia and conjunctivitis were only prevalent in about 25% of the cases. There was, however, a significant heterogeneity in these estimates among the selected studies as shown by the I^2 index values that were varied from 68.8% to 99.6% (Table 2). Except in studies reporting the rates of ventriculomegaly, Egger's test analysis of publication bias (Supplementary Table 4) demonstrated a non-symmetrical distribution for the effect size of each study within the individual congenital disease on either side of the pooled estimates. Egger's test was only non-significant ($p = 0.061$) for studies on ventriculomegaly but significant ($p < 0.001$) for studies on microcephaly, brain calcification and ocular and joint abnormalities. This suggests evidence of publication bias

Table 1 Characteristics of selected studies

Study ID	Country	Dates of recruitment	Design	Population	Number of mothers ($n = 4683$)	Objective
Adams et al., 2016	Puerto Rico	11.15–07.16	Epidemiological report	Pregnant women in Puerto Rico	672	Update on the prevalence of Zika virus infection among pregnant women.
Adhikari et al., 2017	USA	03.16–10.16	Prospective, observational	Pregnant Hispanic women receiving prenatal care for travel to area with active Zika transmission	29	Report the baseline prevalence of travel-associated Zika infection in pregnant women, determine travel characteristics of women with evidence of Zika infection and evaluate the maternal and neonatal outcomes.
Aragao et al., 2017	Brazil	12.15–11.16	Retrospective study	Infants with congenital Zika syndrome 1 year of age or younger	19	Review neuroimaging of infants to detect cases without microcephaly and compare them with those with microcephaly.
Besnard et al., 2016	French Polynesia	10.13–03.14	Retrospective, case series	Infants of pregnancies beginning between June 2013 and August 2014	19	Detecting congenital cerebral malformations and dysfunction in fetuses and newborns.
Bhatnagar et al., 2017	USA, Brazil, Colombia	12.15–07.16	Case series, tissue analysis	Pregnant women suspected with Zika virus infection	32	Investigating the mechanisms of Zika virus intrauterine transmission, replication and tropism and persistence.
Brasil et al., 2016	Brazil	09.15–05.16	Prospective, cohort study	Pregnant women presented to acute febrile illness or rash	116	Characterizing the spectrum of ZIKV disease in pregnant women and infants.
Gregianini et al., 2017	Brazil	10.15–12.16	Epidemiological report	Pregnant women with suspected ZIKV infection	6	Surveillance of Zika infection and microcephaly associated with congenital infection.
Guillmette-Artur et al., 2016	French Polynesia	06.13–05.14	Retrospective, case series	Fetuses with intrauterine Zika virus infection	3	Analyzing the MRI cerebral findings in fetuses with intrauterine Zika virus infection.
Hall et al., 2017	USA	01.16–07.17	Epidemiological report	Pregnant women with confirmed ZIKV infection	15	Surveillance of the Zika virus-associated neonatal birth defects.
Hamer et al., 2017	Americas	01.13–02.16	Case series	Recently travelled pregnant women with confirmed, probable or clinically suspected Zika infection	4	Describing the clinical manifestations and epidemiology of Zika infection in exposed travellers.
Honein et al., 2017[24]	USA	01.15–09.16	Prospective, cohort study	Completed pregnancies with maternal, fetal or infant evidence of possible Zika infection	442	Estimating the proportion of fetuses or infants with birth defects after maternal Zika virus infection by trimester of infection and maternal symptoms.
Kam et al., 2017	Brazil	02.16–08.16	Prospective, cohort study	Acute ZIKV-infected adult patients	6	Investigating the clinical and immunological response in acute ZIKV-infected patients.
Meaney-Delman et al., 2016a	USA	08.15–02.16	Epidemiological report, case series	Pregnant travellers with laboratory-confirmed Zika disease	9	Update on the prevalence of Zika virus infection among pregnant women.
Meaney-Delman et al., 2016b	USA	N/R	Case series	Pregnant women who had travelled to or lived in area with active Zika transmission	5	Investigating the clinical and laboratory characteristics of pregnant women with Zika virus RNA in serum.
Millet et al., 2017	Spain	01.16–12.16	Cross-sectional, population-based	Imported pregnant ZIKV cases reported to Public Health Agency of Barcelona	6	Describe the diagnosed ZIKV cases and analyze the surveillance, prevention and control measures.
Rao et al., 2017	USA	01.16–08.16			5	

Table 1 (continued)

Study ID	Country	Dates of recruitment	Design	Population	Number of mothers ($n = 4683$)	Objective
			Longitudinal, observational study	Pregnant women who had travelled to or had sexual contact with a person who travelled to an area with active Zika transmission		Evaluating pregnant patients with potential exposure to Zika virus infection.
Raegan-Steiner et al., 2017[30]	USA	01.16–12.16	Epidemiological report	Completed pregnancies reported to US Zika Pregnancy Registry	449	Examining placental and fetal tissue specimens for Zika virus infection.
Reynolds et al., 2017	USA	01.16–12.16	Epidemiological report	Completed pregnancies with laboratory-confirmed Zika virus infection reported to US Zika Pregnancy Registry	250	Analysis of completed pregnancies with laboratory evidence of possible Zika virus infection reported in 2016.
Schaub et al., 2017	Martinique	01.16–11.16	Prospective, case series	Pregnant women with suspected Zika infection or any fetal abnormalities at ultrasound examination	551	Prospective analysis of fetal and maternal fluids and tissues in fetuses with confirmed Zika virus infection cases.
de Oliveira-Szejnfeld et al., 2016	Brazil	06.15–05.16	Retrospective, review	Patients with rash occurring during pregnancy or suspected fetal CNS abnormality	16	Document the imaging findings associated with congenital Zika virus infection.
Sohan and Cyrus, 2017	Trinidad and Tobago	03.16–09.16	Observational, case series	Pregnant women infected with Zika in limited-resource setting	100	Evaluating the fetal brain in pregnant women infected with Zika virus in a limited-resource setting.
Zambrano et al., 2017	Ecuador	06.16–07.16	Case-control study	Pregnant women in third trimester of pregnancy	32	Examining the presence of ZIKV in both plasma and cervical cytology of pregnant women.
Zin et al., 2017	Brazil	01.16–10.16	Descriptive, case series	Mother-infant pairs with PCR-confirmed Zika virus infection in maternal specimens	112	Evaluating eye findings in infants with confirmed Zika virus infection during pregnancy.
Pacheco et al., 2016	Colombia	08.15–04.16	Epidemiological report	Pregnant women with clinical symptoms of Zika disease	1484	Clinically assessing patients and evaluated infant microcephaly.
Pomar et al., 2017	French Guiana	01.16–07.16	Prospective, cohort study	Pregnant women with biologically confirmed ZIKV infection	301	Establishing the incidence of fetal central nervous system anomalies, congenital infection and fetal loss in pregnant women infected with ZIKV.

Table 2 Prevalence of the maternal symptoms of Zika virus infection

Study ID	Prevalence (%)					
	Maculopapular rash	Fever	Conjunctivitis	Arthralgia	Headache	Myalgia
Adhikari et al., 2017	80	40	40	40		
Aragao et al., 2017	58					
Bhatnagar et al., 2017	94	59	13	28	19	
Brasil et al., 2016	89.9	27.4	57.5	62.3		40.8
Gregianini et al., 2017	83	65	18	43		38
Hamer et al., 2017	100	50	25	50	75	25
Kam et al., 2017	66.7	33.3		33.3	66.7	16.7
Meaney-Delman et al., 2016a	100	77.8		75	50	50
Meaney-Delman et al., 2016b	80	60		40	20	20
Rao et al., 2017[29]	5.4	4.9	1.6		2.7	2.7
de Oliveira-Szejnfeld et al., 2016	81.3					
Sohan and Cyrus, 2017	100					
Overall prevalence ± SE (%)	76.9 ± 14.5	45.5 ± 11.3	24.6 ± 10.9	46.4 ± 6.9	31.8 ± 10.6	26.6 ± 10.5
95% CI	48.5–105.3	23.4–67.7	3.2–45.9	32.9–60.0	10.9–52.6	6.1–47.1
τ^2	0.24	0.09	0.06	0.02	0.04	0.06
Q	2739	215	173	22	31	120
I^2	99.6	96.3	97.1	68.8	84.0	95.0

in the studies reporting rates of microcephaly, brain calcification, ocular abnormalities and joint abnormalities in infants from ZIKV-infected mothers.

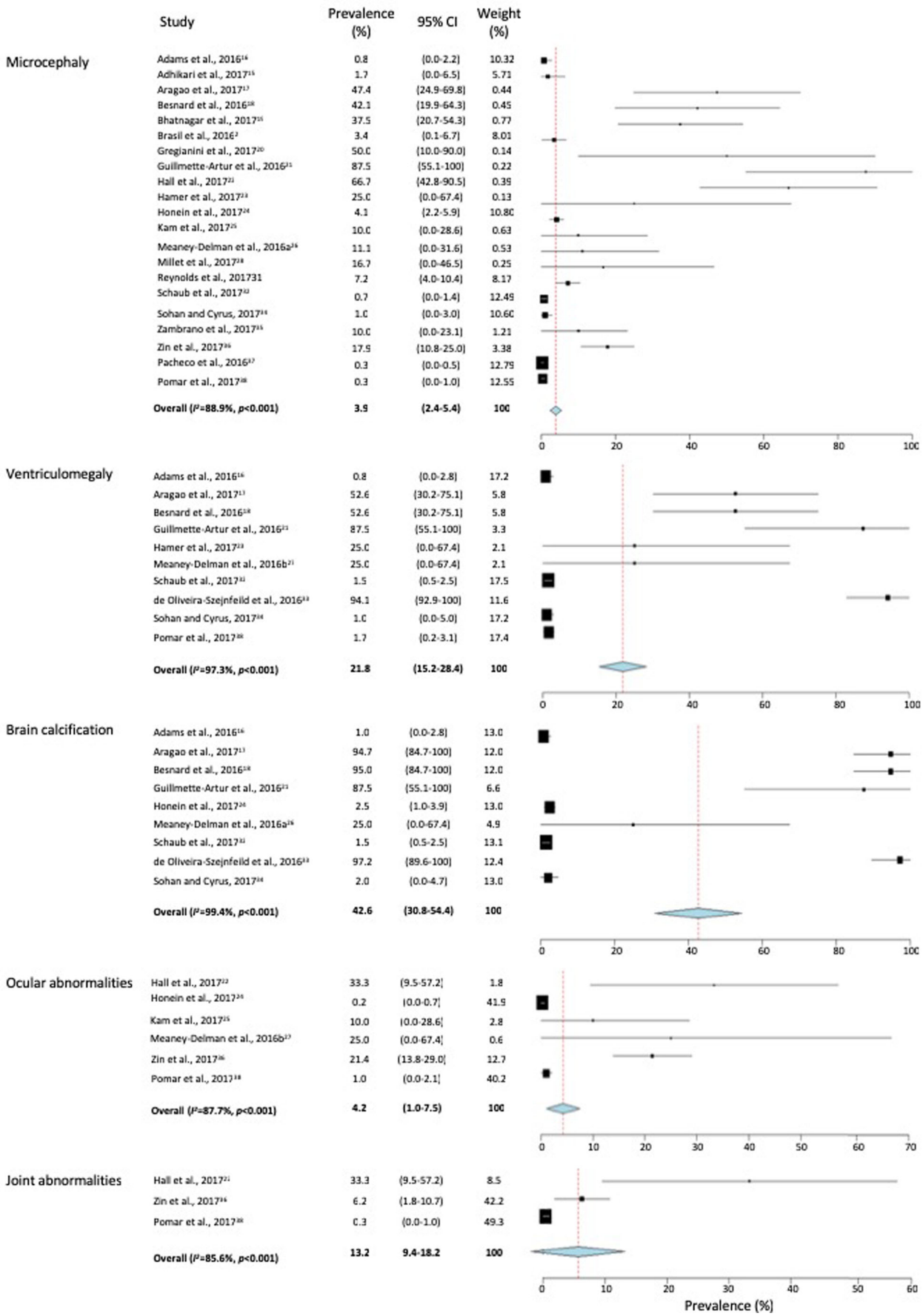
Microcephaly, ventriculomegaly, brain calcification and ocular and joint abnormalities were the congenital disorders reported in at least three of the selected studies. The prevalence of microcephaly, however, was reported in 21 of the 25 selected studies (84%) whereas joint abnormalities were only reported in 3 studies (12%), as shown in Fig. 2. Meta-analysis of the prevalence (%) of congenital disorders in infants of ZIKV-infected mothers (Fig. 2) showed that the most prevalent congenital disorder was brain calcifications (42.6; 95% CI, 30.8–54.4), followed by ventriculomegaly (21.8; 95% CI, 15.2–28.4), joint abnormalities (13.2; 95% CI, 9.4–18.2), ocular abnormalities (4.2; 95% CI, 1.0–7.5) and microcephaly (3.9; 95% CI, 2.4–5.4). The proportions of the evaluated congenital disorders were varied by approximately 100-fold among the identified studies with brain calcifications showing the highest among-studies variability (167-fold). This wide variation in the proportion of congenital disorders from one study to the other may have resulted in the significant among-studies heterogeneity where I^2 index ranged from 85.6–99.4% ($p < 0.001$).

Discussion

This study evaluates the prevalence of a number of congenital disorders in infants of mothers infected with ZIKV during pregnancy. Analysis of the selected reports has shown that brain calcification (42.6%), ventriculomegaly (21.8%), joint abnormalities (13.2%), ocular abnormalities (4.2%) and microcephaly (3.9%) are the most prevalent congenital diseases in infants of ZIKV-infected mothers.

Various pathways were proposed for such a vertical transmission by which the virus crosses the placental barrier and enters the fetal neural tissue. These include the viral invasion to the local dendritic cells and eventually the placenta (Krause et al. 2017) causing damage to the placental barrier (Quicke et al. 2016), the viral entry into the neural progenitor cells via the AXL receptors (Faizan et al. 2016), and/or the viral spread from basal and parietal decidua to chorionic villi and amniochorionic membranes to attack fetal tissues (Tabata et al. 2016), and altering the methylome of neural genes to damage the developing brain (Janssens et al. 2018).

The prevalence of microcephaly (3.9%) appears to be low despite being a well-known sequelae of the maternal ZIKV infection. However, when comparing this prevalence with that in the general population, the difference is significant. A study in Europe examining the prevalence of microcephaly in the general population reported a prevalence of only 1.53 per 10,000 births in 2012 (Morris et al. 2016). This study, however, concluded that there is a significant increase in the prevalence of microcephaly due to the Zika virus of a similar magnitude to those observed in endemic regions such as Brazil (Morris et al. 2016). It may also be worth noting that we observed a significant among-studies variation in the prevalence of microcephaly. This may be attributed to the


Study
Prevalence (%)
95% CI
Weight (%)
Microcephaly
Adams et al., 2016 0.8 (0.0-2.2) 10.32
Adhikari et al., 2017 1.7 (0.0-6.5) 5.71
Aragao et al., 2017 47.4 (24.9-69.8) 0.44
Besnard et al., 2016 42.1 (19.9-64.3) 0.45
Bhatnagar et al., 2017 37.5 (20.7-54.3) 0.77
Brasil et al., 2016 3.4 (0.1-6.7) 8.01
Gregianini et al., 2017 50.0 (10.0-90.0) 0.14
Guilmette-Artur et al., 2016 87.5 (55.1-100) 0.22
Hall et al., 2017 66.7 (42.8-90.5) 0.39
Hamer et al., 2017 25.0 (0.0-67.4) 0.13
Honein et al., 2017 4.1 (2.2-5.9) 10.80
Kam et al., 2017 10.0 (0.0-28.6) 0.63
Meaney-Delman et al., 2016a 11.1 (0.0-31.6) 0.53
Millet et al., 2017 16.7 (0.0-46.5) 0.25
Reynolds et al., 201731 7.2 (4.0-10.4) 8.17
Schaub et al., 2017 0.7 (0.0-1.4) 12.49
Sohan and Cyrus, 2017 1.0 (0.0-3.0) 10.60
Zambrano et al., 2017 10.0 (0.0-23.1) 1.21
Zin et al., 2017 17.9 (10.8-25.0) 3.38
Pacheco et al., 2016 0.3 (0.0-0.5) 12.79
Pomar et al., 2017 0.3 (0.0-1.0) 12.55
Overall (I^2=88.9%, p<0.001) 3.9 (2.4-5.4) 100
0 20 40 60 80 100
Ventriculomegaly
Adams et al., 2016 0.8 (0.0-2.8) 17.2
Aragao et al., 2017 52.6 (30.2-75.1) 5.8
Besnard et al., 2016 52.6 (30.2-75.1) 5.8
Guilmette-Artur et al., 2016 87.5 (55.1-100) 3.3
Hamer et al., 2017 25.0 (0.0-67.4) 2.1
Meaney-Delman et al., 2016b 25.0 (0.0-67.4) 2.1
Schaub et al., 2017 1.5 (0.5-2.5) 17.5
de Oliveira-Szejnfeild et al., 2016 94.1 (92.9-100) 11.6
Sohan and Cyrus, 2017 1.0 (0.0-5.0) 17.2
Pomar et al., 2017 1.7 (0.2-3.1) 17.4
Overall (I^2=97.3%, p<0.001) 21.8 (15.2-28.4) 100
0 20 40 60 80 100
Brain calcification
Adams et al., 2016 1.0 (0.0-2.8) 13.0
Aragao et al., 2017 94.7 (84.7-100) 12.0
Besnard et al., 2016 95.0 (84.7-100) 12.0
Guilmette-Artur et al., 2016 87.5 (55.1-100) 6.6
Honein et al., 2017 2.5 (1.0-3.9) 13.0
Meaney-Delman et al., 2016a 25.0 (0.0-67.4) 4.9
Schaub et al., 2017 1.5 (0.5-2.5) 13.1
de Oliveira-Szejnfeild et al., 2016 97.2 (89.6-100) 12.4
Sohan and Cyrus, 2017 2.0 (0.0-4.7) 13.0
Overall (I^2=99.4%, p<0.001) 42.6 (30.8-54.4) 100
0 20 40 60 80 100
Ocular abnormalities
Hall et al., 2017 33.3 (9.5-57.2) 1.8
Honein et al., 2017 0.2 (0.0-0.7) 41.9
Kam et al., 2017 10.0 (0.0-28.6) 2.8
Meaney-Delman et al., 2016b 25.0 (0.0-67.4) 0.6
Zin et al., 2017 21.4 (13.8-29.0) 12.7
Pomar et al., 2017 1.0 (0.0-2.1) 40.2
Overall (I^2=87.7%, p<0.001) 4.2 (1.0-7.5) 100
0 10 20 30 40 50 60 70
Joint abnormalities
Hall et al., 2017 33.3 (9.5-57.2) 8.5
Zin et al., 2017 6.2 (1.8-10.7) 42.2
Pomar et al., 2017 0.3 (0.0-1.0) 49.3
Overall (I^2=85.6%, p<0.001) 13.2 9.4-18.2 100
0 10 20 30 40 50 60
Prevalence (%)

◀ **Fig. 2** Meta-analysis of the proportion of congenital disorders in infants born to Zika virus-infected mothers. Weights were calculated from binary random effects model analysis. Values represent proportions of microcephaly, ventriculomegaly, brain calcifications, ocular abnormalities and joint abnormalities with 95% confidence intervals.

clustering of observations around the trimesters of maternal infection. When the mother is infected in the third trimester, there are fewer congenital disorders in the infant as most of the development already occurred. As such, Zika risk for birth defects was recently reported to drop for each trimester (Reynolds et al. 2017). Similarly to microcephaly, the global prevalence of fetal ventriculomegaly was estimated to be approximately 0.06% (Isaacs et al. 2018), a figure markedly lower than 21.8% reported here in infants of ZIKV-infected mothers. Idiopathic basal ganglia calcification (Fahr's disease or simply brain calcification) is a genetic condition characterized by calcification in the basal ganglia, especially the globus pallidus, and with occasional involvement of the internal capsule, thalamus and cerebral white matter (Manyam 2005). Although a rare disorder in the general population (Kıroğlu et al. 2010), a recent study reported that among the most common findings in fetuses and infants of laboratory-confirmed ZIKV mothers, brain calcification was present in 92% of the cases (Sanz Cortes et al. 2018). This figure is comparable with many of the reports assessed here, i.e., prevalence of 88–97% (Aragao et al. 2017; Besnard et al. 2016; Guillemette-Artur et al. 2016; Soares de Oliveira-Szejnfeld et al. 2016). A recent review reported that central nervous system calcifications (92.9%), ventriculomegaly (63.1%), microcephaly (39.7%) and ocular findings (2.7%) are among the most common congenital disorders in infants from ZIKV-infected mothers (Marques et al. 2019). These estimates, although in agreement with the order of prevalence of condition in our finding, are markedly higher than those reported here. That study did not conduct meta-analysis to generate these estimates but used overall percentages of a given condition from the total number of assessed cases.

The current study has several limitations. The identified reports had a wide among-studies variance in the proportion of the congenital disorders, which may have contributed to the observed significant heterogeneity. Sources of heterogeneity may also be due to the large variation among studies in the sample size and the different study designs, objectives and outcome measures. Also, the different methodologies used to define how exposure and outcome in mothers and infants were confirmed may have contributed to the large variation and publication bias observed here. This may have led to overestimating the prevalence of the reported congenital disorders. Another limitation is that most of the selected studies were epidemiologic reports that only presented the frequency of the congenital disorders of interest. Furthermore, including only English-language articles might have influenced the publication bias and may have led to missing important data relative to the prevalence of congenital disorders in infants born from infected mothers. Although the search was done only to the end of October 2017, not to include articles published in 2018 might not have compromised the meta-analysis given the different number of cases reported in these years with lower cases in 2018. The selected studies did not provide much insight into biochemical or immunological evidence that could have potentially provided valuable information on the vertical transmission. However, various mechanisms were separately proposed (Krause et al. 2017; Quicke et al. 2016; Faizan et al. 2016; Tabata et al. 2016; Janssens et al. 2018) as mentioned above to include the invasion to the local dendritic cells and placenta (Krause et al. 2017; Quicke et al. 2016), influence on the AXL receptors (Faizan et al. 2016) and spreading to chorionic villi and amniochorionic membranes to the fetal tissues and the developing brain (Tabata et al. 2016; Janssens et al. 2018). Additionally, the congenital disorders examined here are not comprehensive as there was not enough information in the selected studies to assess other diseases (e.g., meningoencephalitis, paraplegia, hyperechogenicity, epileptic seizures (Alves et al. 2016), ophthalmological findings (Ventura et al. 2016)) and provide estimates with any meaningful conclusion. Furthermore, our study did not evaluate the developmental delays since the recruited infants were born after 2015 and the timeline is small to diagnose this condition.

Conclusion

The current study highlights the high prevalence of a range of congenital disorders in newborns of mothers infected with ZIKV. It is critical to continue to follow up on those infants for further evaluation and future studies. Longitudinal assessments will allow for understanding of the vertical pathogenies of ZIKV infection. Studies can also be conducted to clarify the mechanisms by which congenital disorders occur in response to the viral infection during pregnancy and its vertical transmission to investigate the prevalence of viremia in the newborns as it may shed some light on their predisposition to these conditions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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