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Viral infections in stillbirth: a contribution underestimated in Mexico?

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Abstract

Objectives: To analyze the role of viral infections as etiology of stillbirths in Mexico and their epidemiological impact in the context of the global Every Newborn Initiative.
Methods: A comprehensive literature search was performed in electronic databases related to stillbirth and viral infections published prior to January 19th 2021. Stillbirths records and causes from National Mexican databases, during 2008–2019 period were also computed.
Results: Only two articles with a direct relationship between viral infection and stillbirth were found, and one article with an indirect serological association was identified. During the analyzed period there were 198,076 stillbirths, with a National stillbirth rate (SBR) ranging from 6.9 to 6.5 between 2008 and 2014, with a subsequent increase to reach 7.7 in 2019. Only 19 cases were attributed to viral causes and a specific virus was identified in 11. The main causes of early stillbirth were a fetus with premature rupture of membranes and light for gestational age, and for late stillbirth these were fetus affected by oligohydramnios and slow fetal growth. The percentage classified as unspecified deaths varied from 34.4-41.9%.
Conclusions: In Mexico, there has been an increase in SBR during last years, but the goals of the Every Newborn Initiative is met. More than 14,500 stillbirths with at least 5,100 unspecified cases have been reported per year, and only 11 cases were attributable to a specific virus, highlighting the serious underestimation of cases and the need of implementation of routine viral diagnosis methods to improve the care of this global health problem.

Keywords: fetal death cause; Mexico; stillbirth; viral infections.

Introduction

One stillbirth, defined by the World Health Organization as the death of a fetus with a gestational age of at least 28 weeks or with a birth weight of 1,000 g or more, occurs every 16 s worldwide [1]. This means that every year, about two million babies are stillborn without considering the cases occurring at earlier gestational ages [1]. The absence of an identified etiology leads to the risk of recurrence, which can cause depression and financial consequences for parents as well as long-term economic repercussions for society [2].

Stillbirth rate is a sensitive indicator of quality of care in pregnancy and childbirth and a marker of a health system's strength [3]. On average, the risk of a stillbirth is 7.6 times higher in low-income countries (22.7 stillbirths per 1,000 total births) than in high-income countries (3.0 stillbirths per 1,000 total births) [1].

The Every Newborn: An Action Plan to End Preventable Deaths, published by the World Health Organization, sets out a clear vision of how to improve newborn health and prevent stillbirths by 2035 [4]. By this year, the goal is that all countries will reach the target of 10 or fewer stillbirths per 1,000 total births [4]. The Plan proposes registration of stillbirths and newborn deaths accompanied by categorization of the causes of deaths for national and global milestones [4].

In high resource countries as Australia and the United Kingdom, approximately 40% of stillbirths are of unknown aetiology [5, 6]. Despite medical advances, maternal infection remains as a significant cause of perinatal and infant mortality, contributing to 10–25% of stillbirths in high-income countries [7] and 8–50% in low- and middle-income countries [8, 9]. Considering infections, as cause

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of stillbirth, the role of viruses has been less studied or described, despite their potential contribution to a significant proportion of deaths [6].

Among the viruses reported as cause of fetus damage during an infection in the pregnancy, are the rubella virus, measles, cytomegalovirus (CMV), varicella zoster (VZV), herpes simplex virus (HSV), parvovirus B19 (PVB19) and the human immunodeficiency virus (HIV). In addition, Cocksackie A and B viruses, echovirus, enterovirus, hepatitis E, poliovirus, Ljungan virus, dengue virus, lymphocytic choriomeningitis virus and SARS-CoV-2 have also been reported to have impact on perinatal outcome [5, 6, 10, 11].

In Mexico, the causes of fetal death are poorly studied, and are mainly focused on the analysis and description of the social, economic, or gynecological-obstetric factors [12–17]. In this context, there is not a systematized identification of virus as a cause of fetal death. However, high seroprevalences (65.6–97%) of virus related with fetal death, as CMV, have been reported in pregnant women of three States of Mexico [18–20]; highlighting the high risk that these viruses may be associated with stillbirth. In 2015 the National Institute of Statistics and Geography (INEGI, Mexican institution responsible for the statistical and geographical situation) estimated a total of 119,938,473 inhabitants, establishing Mexico as the 10th most populated nation in the world [21, 22]. Considering that Mexico is a country with upper-middle income, the estimation of stillbirth is one in 143 births [1]. These data show that Mexico has a high birth rate and therefore a high risk of developing maternal and neonatal diseases, with viral infections as one of the most probably causes of stillbirth. Here we made a literature review and analyze the epidemiological data of stillbirths and viral infections in Mexico to highlight current epidemiology status and their impact on the public health system as well as the importance of implement screening and prevention politics.

Materials and methods

Literature search strategy and selection criteria

A literature search was performed to identify the published studies having data of viral infections related to stillbirths in Mexico. Using combinations of the keywords: “stillbirth”, “Mexico”, “fetal death” and “virus”, and their Spanish translations as well, we searched studies published prior to January 19th 2021 (there was no lower limit on the date) in databases both in English as in Spanish: PubMed, Elsevier, Scielo, Imbiomed, LILACS, BiDi and TESIUNAM (UNAM Databases). Articles containing data from Mexico were included. Studies related to postnatal infections, diagnosis, Genetics, Psychology, obstetric risk factors, other microorganisms than virus, non-human species, and information about other countries than Mexico were excluded. Articles were screened based on the titles and abstracts by two researchers, and then, based on full-text versions. The flowchart of the literature search strategy is shown in Figure 1.

Stillbirths analysis of Mexican databases

We downloaded official data available of stillbirths in Mexico covering 2008 to 2019 from INEGI website. Information about gestational age and cause of fetal death were obtained and fetal deaths with unknown weeks of gestation were not considered for this study.

We defined a stillbirth as a fetal death that occurred at or after 21 weeks of gestation; stillbirths were further classified as early (between 21 and 27 weeks) and late (at 28 weeks and later) [17]. Stillbirth rate (SBR) was defined as the number of fetal deaths per 1,000 total births (live or dead) and calculated as:

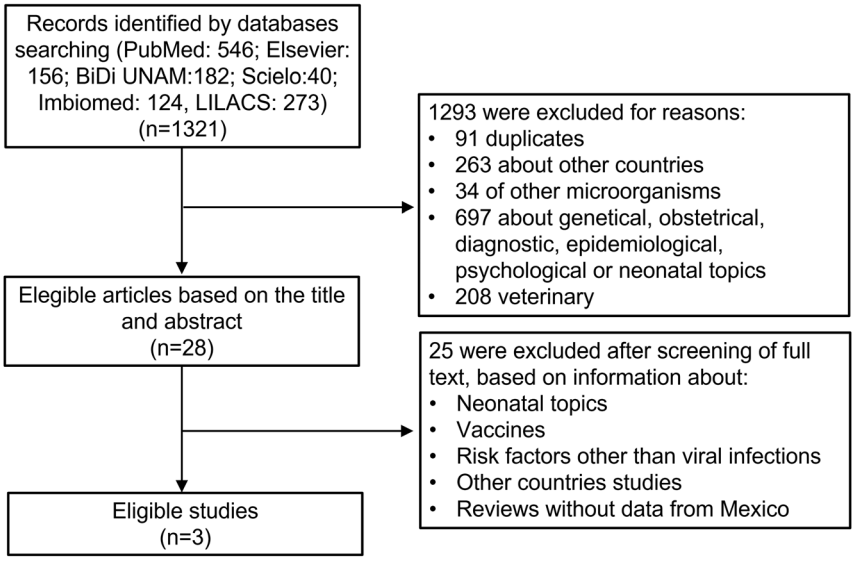

Figure 1: Flow chart showing the process of literature selection.

$$SBR = 1000 \times \frac{sb}{sb + lb}$$

sb refers to the number of stillbirths and lb refers to the number of live births regardless of gestational age.

Regarding the cause of fetal death recorded in INEGI website, we selected some classifications of the Chapter XVI (certain conditions originating in the perinatal period, P00-P96), of International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and grouped as conditions with viral infection diagnosed, conditions probably related to viral infections (PRVI) and classifications with an unspecified diagnosis (Supplementary Table 1). The PRVI subgroup contains pathological findings that can be originated by a viral infection. Conditions diagnosed with other microorganisms (bacteria, parasites, fungi) were not considered in this study.

Statistical analysis

To analyze variations in the National stillbirth rate between 2008 and 2019, we used a sequential analysis technique based on a control chart with the national stillbirth mean for that period and standard deviation (SD) as upper and lower limits. The differences between the number of recorded causes were analyzed by two-way analysis of variance. Differences between causes and years were reported as significant at $p<0.05$.

Results

Literature search results

The literature search identified 1,321 articles from electronic databases. After titles and abstracts of publications were reviewed, 28 articles were initially selected from PubMed, Elsevier, Imbiomed, LILACS, BiDi and Scielo databases. Subsequently, full-text versions were obtained for potentially eligible studies but after a second screening 25 articles were excluded because they were related to neonatal viral infections, vaccines, other countries than Mexico studies, reviews without data from Mexico or maternal risk factors different from viral infections (Figure 1).

The three articles included were written in Spanish and published in 1995 and 2019 [23–25]. In the first one, a serological screening was conducted in a tertiary hospital of Mexico City, where 128 patients considered as high risk of PVB19 infection were analyzed for IgG antibodies, resulting positive 47.6% [20]. Considering the different subgroups analyzed in the study, the greatest positivity was in patients with mononucleosic syndrome, followed by patients with recurrent miscarriage and patients with aplastic anemia (82.7, 60 and 41.6%, respectively) [23]. Twenty-four healthy persons were included as control group, with 12.5% positive for IgG antibodies.

The second article included, is a case report of a 23 years-old female on the ninth week of gestation by last menstrual period and 10.3 weeks by ultrasound [24]. She presented exanthema, myalgia, arthralgia, retroocular pain, and headache and Zika virus infection was confirmed. In her 18.6 weeks a non-mobile single fetus was documented, with microcephaly, lack of thorax with cardiac activity, anterior corporal placenta with 30% of calcification, and an image of probable venous lake vs. placental cyst [24]. The woman was admitted for late abortion and congenital Zika syndrome was diagnosed (Zika virus was positive in umbilical cord and negative for toxoplasmosis, rubella, CMV, HSV and HIV).

The third article is a case report of a 31 years-old female, with 32 weeks of gestation, attended in a medical service due to a non-quantified fever, headache, retro-orbital pain, myalgias and arthralgias of three days of evolution [25]. Upon the admission to the hospital, the diagnosis of non-severe dengue due to NS1 positive was confirmed. Later, she persisted with fever, deterioration of the hemodynamic state, circulatory collapse, vascular placental involvement and, as a result, fetal and maternal death [25].

Stillbirths analysis of Mexican databases results

Our analysis included data from Mexican databases covering a 12-year period (2008–2019). These data were previously systematically collected and compiled by the INEGI. A total of 198,076 cases of stillbirth at or after 21 weeks of gestation were reported in Mexico during the period analyzed; 2008 recorded the highest number of stillbirths (18,187 cases) and a decrement per year was observed until 2018 (14,565 cases) with an increase for 2019 (16,284 cases), similar tendencies were observed for late (squares) and total (circles) stillbirth (Figure 2A).

When the total SBR is calculated (fetal death registered at ≥12 weeks), a gradual increase is observed until reach the maximum record in 2019 with more than 2 SD with respect to the national mean (Figure 2B). For SBR and late SBR, a slight decrease can be observed from 2008 to 2014, with marginal fluctuation until 2019 where a significant increase is observed (up to 3 SD and 1 SD, respectively, Figure 2C and D).

The overall percentage of fetal deaths with unknown gestational age during 2008–2019 was 0.3% (854 of 23,154 total cases ≥ 12 weeks). The above does not have a high impact on total cases, however, a fact to highlight is that the lack of gestational age registration has been decreasing, with an average of 114 cases between 2008 and

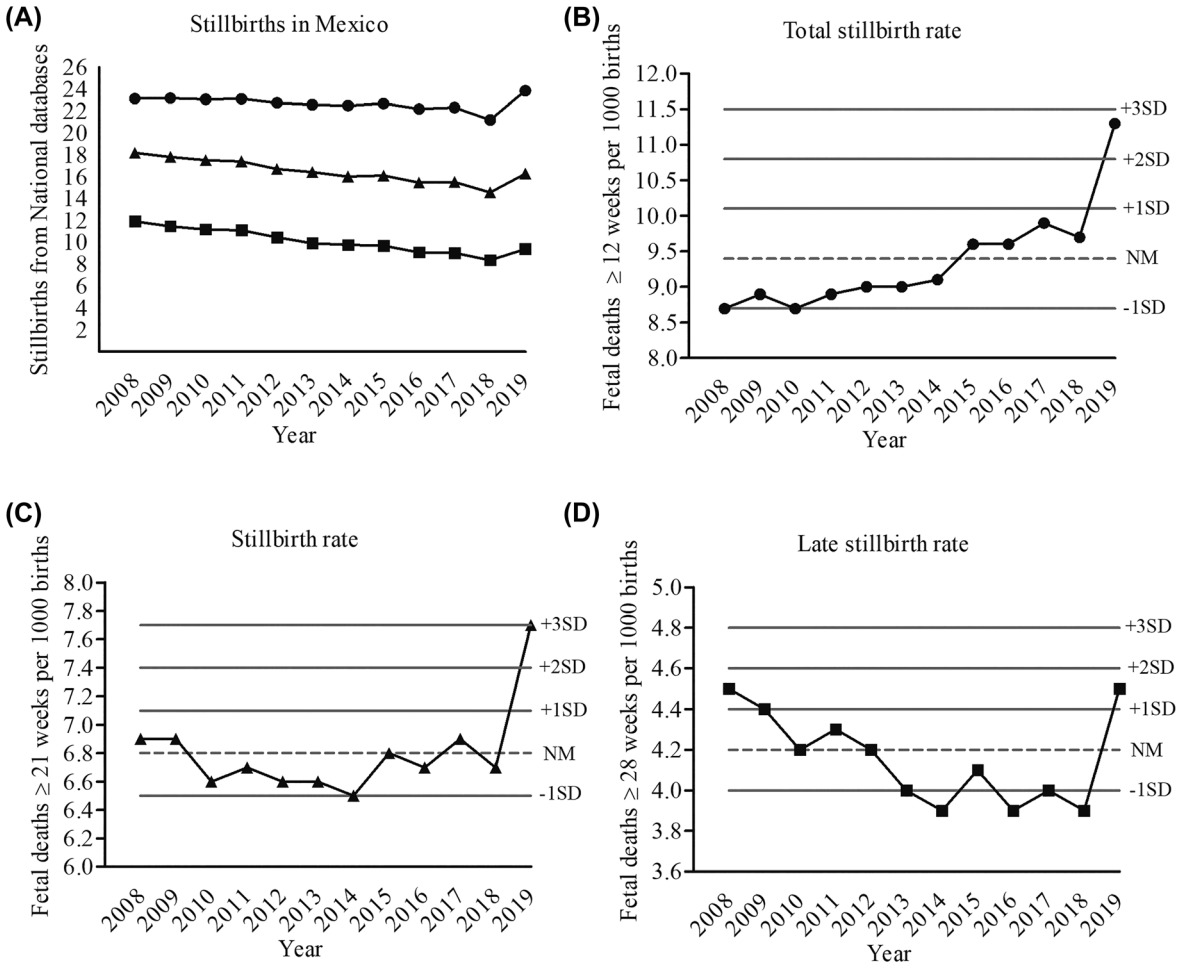

Figure 2: Stillbirths records (A), total stillbirth rate (B), stillbirth rate (C) and late stillbirth rate (D) in Mexico during the 2008–2019 period. The graphs were elaborated with data of stillbirth ≥12 weeks of gestation (circles), stillbirth ≥21 weeks (triangles) and late stillbirth ≥28 weeks (squares). NM, national mean; SD, standard deviation of national mean. Data plotted in (A) ×1,000.

2014 to only 11 average cases between 2015 and 2019 (Supplementary Table 2).

We calculated the SBR for each state conforming Mexico using data of 2019 and considering the fetal death at ≥12 weeks (Supplementary Table 3). The highest SBR was recorded in Mexico City (21.1), followed by the State of Mexico (18.0) and Aguascalientes (15.4); while Oaxaca, Sinaloa and Guerrero had the lowest rate (6.2, 5.9 and 4.9, respectively).

Figure 3A shows the causes of stillbirth at ≥21 weeks, according to the classification of Chapter XVI (P00-P96, Certain conditions originating in the perinatal period) of CIE-10. The most P00-P96 causes were recorded in 2008 with 16,702 cases and the lowest was recorded in 2018 with 13,555 cases.

The PRVI subgroup varies from 12.9 to 17.2% of the total of P00-P96 causes while the Unspecified subgroup varies from 34.4 to 41.9% (Figure 3A). Cases of viral infections vary from zero to five, being 19 the total number of stillbirth cause during the period analyzed (Figure 3B). Nine cases were identified as congenital CMV infection, one as congenital rubella syndrome and one as congenital viral hepatitis.

The analysis of PRVI subgroup shows that P01.1 (Fetus and newborn affected by premature rupture of membranes) is the most frequent cause occurred in early stillbirth, with more than 700 cases per year, except for 2014 and 2018 with 670 and 687 cases respectively (Figure 4A). The second cause of the PRVI subgroup is P05.0 (Light for gestational age) with 207 cases in 2008 and 453 in 2019. The third cause is P01.2 (Fetus and newborn affected by oligohydramnios) with values from 99 (in 2012) to 147 cases (in 2019). P02.7 (Fetus and newborn affected by chorioamnionitis, amnioitis, membranitis, placentitis) and P83.2 (Hydrops fetalis not due to haemolytic disease) have similar frequency with values from 59 to 97 cases and

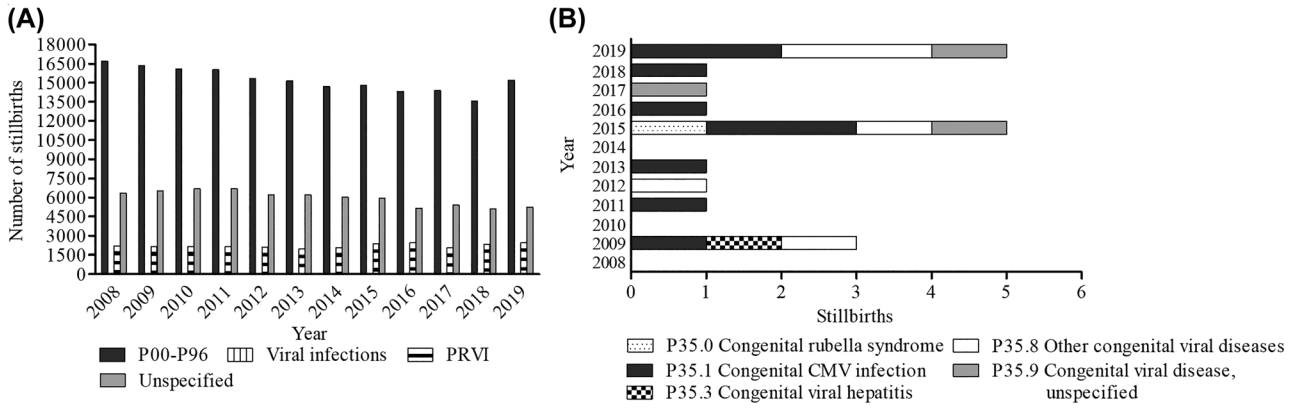

Figure 3: (A) Causes of stillbirth classified in Chapter XVI of ICD-10 (P00-P96) and causes grouped as conditions with viral infection diagnosis (viral infections), conditions probably related to viral infections (PRVI) and classifications with an unspecified diagnosis (unspecified). (B) Causes of stillbirth classified as viral infections.
The graphs were elaborated with data of stillbirths ≥21 weeks of gestation recorded in Mexico during 2008–2019. P00-P96 includes all causes; viral infections include P23.0, P35.0, P35.1, P35.2, P35.3, P35.8 and P35.9; PRVI includes P00.2, P01.1, P01.2, P01.3, P02.7, P05.0, P05.9, P23.9, P39.2, P39.3, P39.8, P39.9, P58.2 and P83.2; unspecified includes P00.9, P01.8, P01.9, P02.9, P95, P96.8 and P96.9.

46 to 82 cases, respectively; followed by P01.3 (Fetus and newborn affected by polyhydramnios) and P00.2 (Fetus and newborn affected by maternal infectious and parasitic diseases) with values from 36 to 57 cases and 8 to 22 cases respectively. P05.9 (Slow fetal growth, unspecified), P23.9 (Congenital pneumonia, unspecified), P39.2 (Intra-amniotic infection of fetus, not elsewhere classified), P39.8 (Other specified infections specific to the perinatal period) and P39.9 (Infection specific to the perinatal period, unspecified) are the ICD-10 causes in early stillbirth with the minimum values (from zero to four, Figure 4A).

With respect to the analysis of PRVI subgroup in late stillbirth, Figure 4B shows that P01.2 (Fetus and newborn affected by oligohydramnios) with 197 (in 2017) to 278 cases (in 2008) and P05.9 (Slow fetal growth, unspecified) with 63 (in 2013) to 343 cases (in 2008), are the most frequent causes. The third cause is P01.1 (Fetus and newborn affected by premature rupture of membranes) with 77 (in 2014) to 178 cases (in 2008); followed by P01.3 (Fetus and newborn affected by polyhydramnios) with 42 (in 2018) to 97 cases (in 2017) and P83.2 (Hydrops fetalis not due to haemolytic disease) with 58 (in 2009) to 85 cases (in 2016).

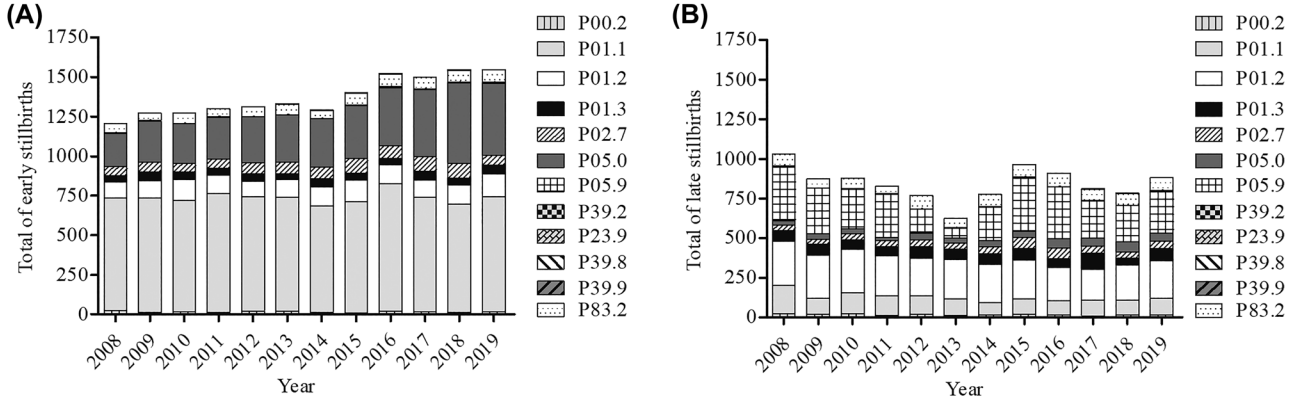

Figure 4: ICD-10 classifications of Chapter XVI grouped as probably related to viral infection (PRVI) recorded in early (A) and late stillbirth (B).
The graphs were elaborated with data of stillbirths ≥21 weeks of gestation recorded in Mexico during 2008–2019. PRVI includes P00.2 (fetus and newborn affected by maternal infectious and parasitic diseases), P01.1 (fetus and newborn affected by premature rupture of membranes), P01.2 (fetus and newborn affected by oligohydramnios), P01.3 (fetus and newborn affected by polyhydramnios), P02.7 (fetus and newborn affected by chorioamnionitis, amnioitis, membranitis, placentitis), P05.0 (light for gestational age), P05.9 (slow fetal growth, unspecified), P23.9 (congenital pneumonia, unspecified), P39.2 (intra-amniotic infection of fetus, not elsewhere classified), P39.3 (neonatal urinary tract infection), P39.8 (other specified infections specific to the perinatal period), P39.9 (infection specific to the perinatal period, unspecified), P58.2 (neonatal jaundice due to infection) and P83.2 (hydrops fetalis not due to haemolytic disease) causes.

The following causes are P02.7 (Fetus and newborn affected by chorioamnionitis, amnioitis, membranitis, placentitis) with 33 (in 2008 and 2008) to 69 cases (in 2015) and P05.0 (Light for gestational age) with 21 (in 2011) and 64 cases (in 2018). P23.9 (Congenital pneumonia, unspecified), P39.2 (Intra-amniotic infection of fetus, not elsewhere classified), P39.8 (Other specified infections specific to the perinatal period) and P39.9 (Infection specific to the perinatal period, unspecified) are the ICD-10 causes in late stillbirth with the minimum values (from zero to four, Figure 4B). For PRVI subgroup, there were significative differences between the causes ($p<0.001$) but there were not significative differences between the years in early ($p=0.12$) and late ($p=0.27$) stillbirth.

The analysis of Unspecified subgroup shows that P96.8 (Other specified conditions originating in the perinatal period) is the most frequent cause recorded in both early (Figure 5A) and late stillbirth (Figure 5B). This cause varies from 1,668 (in 2019) to 2,239 (in 2010) for early stillbirth; and from 2,729 (in 2019) to 4,187 (in 2011) for late stillbirth. P95 (Fetal death of unspecified cause) is the second cause in both early (with 54–171 cases, corresponding to 2012 and 2019 respectively; Figure 5A) and late stillbirth (with 131–368 cases, corresponding to 2012 and 2019 respectively; Figure 5B). P01.8 (Fetus and newborn affected by other maternal complications of pregnancy) is the third cause in both early (with 39–131 cases, corresponding to 2010 and 2019 respectively; Figure 5A) and late stillbirth (with 23–51 cases, corresponding to 2009, 2012 and 2019 respectively; Figure 5B). P96.9 (Condition originating in the perinatal period, unspecified) is the fourth cause in both early (with 3–21 cases, Figure 5A) and late stillbirth (with 6–33 cases, Figure 5B). The following cause is P02.9 (Fetus and newborn affected by abnormality of membranes, unspecified) with zero to 14 cases in early (Figure 5A) and zero to 34 cases in late stillbirth (Figure 5B). P00.9 (Fetus and newborn affected by unspecified maternal condition) and P01.9 (Fetus and newborn affected by maternal complication of pregnancy, unspecified) are the less frequency causes in early and late stillbirth, with zero to 15 cases. For Unspecified subgroup, there were significative differences between the causes ($p<0.001$) but there were not significative differences between the years in early ($p=0.93$) and late ($p=0.66$) stillbirth.

Discussion

In Mexico, even though the virology research has been increasing in the last two decades, the articles published in this area is still limited [26]. Data from our systematic literature review indicate that no articles with high impact related to viral infections and stillbirth has been published prior to January 19th, 2021. Besides, viral infection diagnosis is still missing since only in three articles of our literature search, the authors put focus on the identification of a specific virus (PVB19, Zika and dengue virus) [23–25]. A recently published study reported placental and/or fetal infection as probable cause of death in 15.1% of stillbirths during a three-year period in a tertiary care center of Mexico [27]. The pathogens identified were *Escherichia coli*, *Staphylococcus warnerii*, *Enterobacter* sp, *Klebsiella pneumoniae*, *Listeria monocytogenes*, CMV, *M. tuberculosis*, *Candida albicans*, *Candida krusei* and Zika

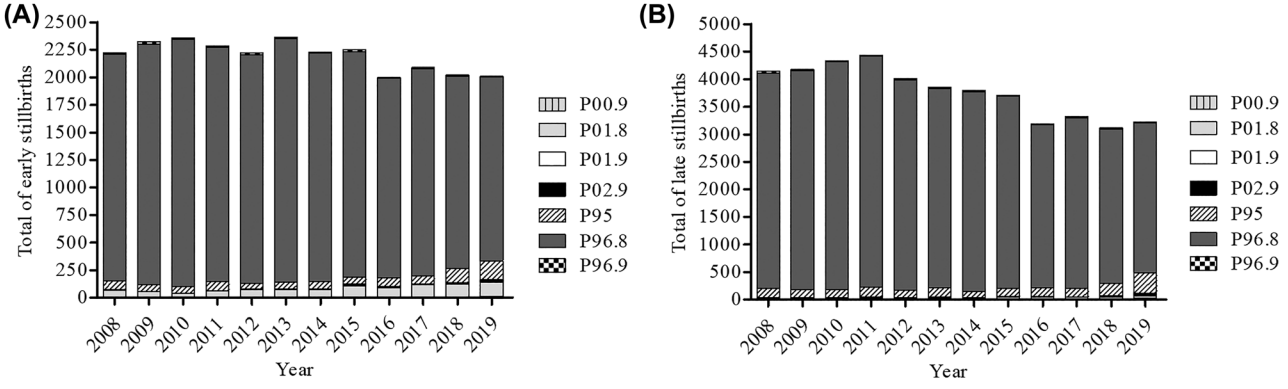

Figure 5: ICD-10 classifications of Chapter XVI grouped as unspecified recorded in early (A) and late stillbirth (B).
The graphs were elaborated with data of stillbirths ≥21 weeks of gestation recorded in Mexico during 2008–2019. Unspecified includes P00.9 (fetus and newborn affected by unspecified maternal condition), P01.8 (fetus and newborn affected by other maternal complications of pregnancy), P01.9 (fetus and newborn affected by maternal complication of pregnancy, unspecified), P02.9 (fetus and newborn affected by abnormality of membranes, unspecified), P95 (fetal death of unspecified cause), P96.8 (other specified conditions originating in the perinatal period) and P96.9 (condition originating in the perinatal period, unspecified).

virus [27]. A former study conducted in a second care center of the north of Mexico, reported that infectious diseases were the etiology of 9% of stillbirths occurring between 1997 and 1998 but does not specify the microorganisms involved [28].

Most of the studies about Mexican population include topics of local and national SBR [15, 17, 29], national data analysis of maternal sociodemographic risk factors [17], stillbirth causes and risk factors of patients of level 2 or Level 3 care centers [12–16, 27–31]; many of them published in Spanish limiting their diffusion worldwide. Overall, these findings highlight the necessity of develop scientific research in Mexico focused on stillbirth.

Stillbirths are reported inconsistently across countries due to the use of different criteria or combinations of criteria and varying thresholds in areas such as gestational age and/or birthweight [1]. In Mexico, stillbirths are registered for 12 weeks of gestation in databases of INEGI; so, we decided to graph three different criteria for number of stillbirth and SBR (Figure 2). Using the criteria that allow international comparisons (28 weeks), 11,217-14,481 cases per year would have been unrecorded during the period analyzed (Figure 2A). This difference is reduced to 4,967–7,584 if stillbirths are considered at or after 21 weeks, showing that the real burden of stillbirths worldwide could be underestimated due to the exclusion of cases occurring at earlier gestational ages.

Our work shows that national SBR (stillbirths per 1,000 total births) in Mexico declined from 2008 to 2014, if stillbirth is considered at 21 or 28 weeks (Figure 2C and D). This is according to previous study in which SBR was analyzed from 2000 to 2013 [17]. Afterwards, national SBR tendency increases until reach the highest record in 2019 with values of 7.7 and 4.5 for SBR and late SBR respectively. This finding is an attention point for public health politics because is necessary to implement measures to reduce and prevent stillbirths.

In 2019, SBR around the world (considered at 28 weeks or more) ranged from 1.4 to 32.2 [1]. In sub-Saharan Africa, the SBR of 21.7 was seven-fold than the lowest regional average SBR of 3.1 found in Europe, Northern America, Australia, and New Zealand [1]. With respect to local SBR, in Mexico the highest values were in the central states of the country (Mexico City and State of Mexico, Supplementary Table 3), the same behavior was observed for 2013 in a previous report [17]. These two states are the most populated of our country, concentrating around the 20% of the total national population [32]. Another study reported SBR of 25.3, 31.8 and 79 for 2008, 2009 and 2010 in a hospital of the State of Mexico [15].

Despite advances in health services to prevent or treat the causes of infant mortality, progress in reducing the SBR has been unsatisfactory worldwide [1]. To help end preventable stillbirths and identify the necessary interventions and resources, it is essential to first understand the causes of death [1]. This is an important point because emphasis to cardiovascular diseases, cancer, and metabolic disorders such as diabetes and obesity has been given in Mexico despite perinatal deaths (P00-P96) have been reported within the top 10 causes of death [33].

In high resource countries such as the United Kingdom, viral infections were the cause of approximately 4.2% of fetal deaths greater than 20 weeks and 13.2% of postneonatal deaths (28–364 days of life) [6]. If we consider 4.2% of stillbirths, 890 to 1,000 cases per year could be estimated for Mexico. These data are surprising since in the last 12 years the total stillbirths associated with viral infections has been 19, being in 2015 and 2019 the greater records (5 in each year, Figure 3B). In addition, a specific virus was identified only in 11 cases with CMV as the most frequent causal agent; showing the necessity of implement viral diagnosis in Mexico to improve health services.

In this work, we analyzed some causes of ICD-10 grouped as "probably related to viral infection (PRVI)" since in Mexico, diagnosis of bacterial infections is available in the most of hospitals, but viral infections diagnosis is less implemented; and considering that some pathologies can be the result of undiagnosed maternal or fetal viral infection [5]. For example, PVB19 occurs worldwide and the risk of hydrops fetalis and fetal death caused by infection is 4–10% when transmission occurs before 20 weeks of gestation [34]. Nonimmune hydrops fetalis, an indicator of severe edema and cardiac deficiency, is diagnosed via ultrasound [34]. So, in this study, the P83.2 cause (Hydrops fetalis not due to haemolytic disease) was included in this group. With respect to CMV, is the most common congenital viral infection in near countries as the United States [34]. Histopathological analysis of term placentas from congenital CMV infection, showed pronounced villous maldevelopment, diffuse villitis, cytomegalic cells, and areas of necrosis and calcification [34, 35]. Pathologic findings suggest underlying CMV infection contributes to idiopathic intrauterine growth restriction [34, 35]; in addition, CMV has been identified in several tissues of fetus with intrauterine death [34–36]. For these reasons, P02.7 (Fetus and newborn affected by chorioamnionitis, amnionitis, membranitis, placentitis) and P05.9 causes (Slow fetal growth, unspecified) were included in PRVI group. CMV is also associated with premature rupture of membranes, CNS disease, low birth, prematurity, microcephaly, hydrocephalus, ventriculomegaly, lissencephaly, polymicrogyria, oligohydramnios, polyhydramnios,

hydrops fetalis, placental damage, among others [5, 35, 37–39]. Other viral agents have been associated with adverse outcomes following vertical transmission: human herpes virus with intrauterine growth restriction, multiorgan disease, deciduitis, villitis; Adenovirus with intrauterine growth restriction and hydrops fetalis; Adeno-associated virus with prematurity; Enterovirus with myocarditis; Zika virus with microcephaly, Epstein-Barr virus with preeclampsia, deciduitis, villitis, etc. [5, 40–43]. In this study, the most frequent causes for early stillbirth were fetus and newborn affected by premature rupture of membranes and light for gestational age while fetus and newborn affected by oligohydramnios and slow fetal growth, unspecified were for late stillbirth.

It was noteworthy that unspecified subgroup had the highest number of cases with thousand recorded in both early and late stillbirth (Figure 3A, Figure 5A and B); this shows that is necessary to improve the quality of post-mortem studies to avoid the absence of diagnosis or discrepancies between clinical and autopsy diagnosis. A previous study in a tertiary level hospital of the north of Mexico, found 41.4% of discrepancies; being pneumonia, followed by sepsis and massive pulmonary hemorrhage associated with prematurity, the most common divergent diagnosis [44]. In addition, is necessary to analyze stillbirth causes because in Mexico the National Plan of Health lacks a program focused on prevention stillbirth; although some institutes, as the National Institute of Perinatology, have implemented internal programs to provide a better care to parents with fetal loss [27].

The Every Newborn Action Plan establish that vital statistics provide indispensable information to make policies more effective and responsive to the needs of women and children within countries [4]. Failure to collect high quality-data of cause of death, results in absence for crucial information for planning and evaluation health services [4]. According to the goal of this initiative, by 2035, all countries will reach the target of 10 or less stillbirths per 1,000 total births. Mexico meets this goal if the international parameter of ≥28 weeks is used as reference; nevertheless, is important to consider the tendency to an increment in SBR of the last years and that many cultural factors as well as a lack of improvement in the notification systems must be considered, which lead to suppose that the total number of cases is underestimated.

Conclusions

This study exhibits the consistently high proportion of stillbirths without recorded cause in the last years, as well as highlights the lack of a systematic and routinary algorithm for detection of viral infection as causative of stillbirth. In addition, we show that the stillbirth registry in Mexico underestimates the impact of viral infections. An important point is the development of public health politics focused on implementing better diagnostic methods, improving the quality maternal care, and reducing the stillbirths in Mexico. In addition, is necessary that more scientists' teams direct research in this field.

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