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Systematic Review

Are fetal arrhythmias associated with maternal influenza viral infections during pregnancy?—A systematic review and report of two cases

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Abstract

Background: Influenza virus infection during pregnancy is associated with adverse pregnancy outcomes, including congenital anomalies early in pregnancy; however, fetal arrhythmias have not been previously described in these pregnant women. In non-pregnant women, influenza viral infections are associated with arrhythmias and limited data exists regarding fetal arrhythmias secondary to maternal influenza infection. **Methods**: We performed an online systematic literature review, using PubMed, Google Scholar and Medline search engines to identify all listed publications that meet our inclusion criteria and identified a total of 40 articles. We reviewed abstracts, case reports, case series, surveillance or outbreak reports and observational cohort studies, and exlcuded non-English articles, as well as any unpublished reports, narrative reviews, irrelevant topics, and letter or editorials. We proposed to answer whether or not there is a possible association between maternal acquisition of influenza infection and fetal arrhythmias? Using the data search engines listed above, we identified a total of 40 articles through this search, of which 39 articles that did not meet our inclusion criteria. Thus, we identified only a single article that illustrated the key findings pertaining to our systematic review. In addition, we describe a case series of two additional cases. **Results**: Three cases were identified that demonstrate a possible association between maternal acquisition of influenza infection and fetal arrhythmias. In our case series, both cases required antiarrhythmic treatment during pregnancy and postnatally to achieve cardioversion to normal sinus rhythm. Neither of these pregnant women received vaccination against influenza at the time of their initial presentation. **Conclusions**: Fetal arrhythmias can lead to adverse pregnancy outcomes and can be treated early to allow for pregnancy prolongation and overall well-being improvement and chance for intact survival for the fetus and neonate. Based on our systematic review findings and current case series described here, we believe that there is a possible association between maternal influenza infection and fetal arrhythmias, thus, it seems reasonable to assess for concurrent maternal influenza infection in cases of fetal arrhythmias should other maternal symptoms be present for this infection. Larger observational studies are needed to assess if there truly is an association and whether or not a causal link can be established.

Keywords: Arrhythmias; Pregnancy; Fetus; Neonate; Influenza

1. Introduction

Influenza virus is a common infection that primarily causes respiratory disease and is divided into four subtypes based on the surface proteins, including types A, B, C and D. Subtypes A and B are associated with seasonal epidemics with only influenza A associated with pandemic disease [1,2]. Influenza A is also further divided into subtypes based on the surface proteins that make up their genes (i.e., H1N1). Subtype C causes transient mild disease and subtype D does not lead to human disease.

During pregnancy, the acquisition of influenza viral infection is associated with adverse pregnancy outcomes including miscarriage, preterm birth, low birth weight and fetal/neonatal death; maternal pneumonia, prolonged hospital admissions, intensive care unit admissions, need for mechanical ventilation and maternal mortality [3–9]. In addition, transient arrhythmias, myocardial infarctions, congestive heart failure, pericarditis and myocarditis that require medical treatment have been reported [10–14]. Influenza vaccination is recommended in all pregnant women in order to reduce risk of these complications [10].

In the non-pregnant population, influenza infections are also associated with adverse cardiovascular events, ranging from arrhythmias which may require treatment, myocardial infarctions, and congestive heart failure [11–13]. These outcomes are secondary to the enhanced proinflammatory cytokine release which subsequently leads to rising fever, hemodynamic changes including hypovolemia and vasodilatation, and cardiopulmonary distress with hypoxic changes [14]. Though the respiratory system is the primary site of infection, influenza can also cause myocarditis and pericarditis [15]. We performed an online systematic literature review, using PubMed, Google Scholar and Medline search engines, related to fetal arrhythmias in

the setting of maternal influenza infections. We identified one publication in which a fetal arrhythmia was diagnosed in a pregnant mother with confirmed influenza A viral infection that was carried to term and the neonate had a transient fetal arrhythmia that resolved without antiarrhythmic treatment [16].

In this manuscript, we describe a case series of two cases during pregnancy in which a fetal arrhythmia was identified and happen to coincide at the same time of a maternal influence infection. In the first case, during the second trimester, this pregnant patient presented with signs and symptoms consistent with influenza infection at the time of her routine anatomy scan. Maternal testing was positive for Influenza B infection. Incidentally, fetal tachycardia was noted and a fetal echocardiogram was performed which was concerning for a fetal supraventricular tachycardia (SVT). Subsequently, this fetus developed evidence of hydrops remote from delivery and decision was made to initiate maternal antiarrhythmic treatment for fetal cardioversion. The pregnant mother was also treated with antiviral treatment (oseltamivir) for treatment of her influenza infection. Successful cardioversion was achieved and the hydrops had resolved. In the second case, this was identified in the early third trimester and similarly to the first case, she presented with signs and symptoms of influenza at the time of her anatomy scan and testing was consistent with Influenza A infection. A fetal echocardiogram was performed concerning for fetal atrial flutter which was sustained on subsequent ultrasound follow up visits. As with the first case, she was treated with maternal antiarrhythmic treatment and oseltamivir with successful cardioversion achieved. Both patients had full term deliveries of live neonates. In addition, through our systemic review, we identified an additional article showing a possible associated between maternal influenza infection and fetal arrhythmias, and thus a total of three cases have been identified.

2. Methods

2.1 Sources

We performed an online systematic literature review, using PubMed, Google Scholar and Medline search engines to identify all listed publications using search terms established: ("influenza" or "influenza infection") and ("arrhythmias" or "pregnancy" or "fetus" or "neonate"). Using a combination of these proposed key words, we found a total of 40 articles through this search and created a Microsoft Excel spreadsheet to create a bibliography of citations and abstracts for review. The original research question that we focused on was whether or not there is a possible association between maternal acquisition of influenza infection during and fetal arrhythmias?

2.2 Study selection

The minimum criteria we required for these articles included the presence of at least 1 case of influenza infection during pregnancy or fetal arrhythmia. For the purposes of inclusion in our systematic review, the diagnosis of influenza infection was established based on the authors' report, regardless of the availability of the reported clinical or laboratory data. We selected the articles that described influenza infection during pregnancy associated with adverse pregnancy outcomes, specifically congenital anomalies. We limited our inclusion to reports or studies on human cases and excluded any animal studies and thus we reviewed abstracts, case reports, case series, surveillance or outbreak reports and observational cohort studies that may pertain to our proposed key words. For the purpose of this review, we did not come across any non-English articles during our search. Lastly, we excluded any unpublished reports, narrative reviews, irrelevant topics, and letter or editorials; however, we did review these articles to see if we can identify any additional sources of primary data that would pertain to this systematic review.

Two reviewers (B.H.R. and J.M.E.) screened the titles and abstracts that pertained to our systematic review and selected those articles. The data elements extracted from the articles included (1) gestational age at the time of diagnosis and delivery; (2) timing of maternal acquisition of influenza infection and whether confirmatory testing was obtained; (3) clinical presentation and findings on prenatal ultrasound if available; (4) subtype of the influenza infection identified; (5) maternal, obstetrical, fetal and neonatal outcomes, including need for medical intervention.

2.3 Tabulation, integration, and results

Using the data search engines listed above, we identified a total of 40 articles through this search and created a Microsoft Excel spreadsheet to create a bibliography of citations and abstracts for review. After we performed a full-text review, we excluded 35 articles based on abstract screening, and an additional 4 articles secondary to either these articles being narrative reviews, irrelevant topics, and letter or editorials. Thus, we identified only a single article that illustrated the key findings pertaining to our systematic review [16]. The authors of this identified single case report described that a fetal arrhythmia was diagnosed in a pregnant mother with confirmed influenza A viral infection that was carried to term and the neonate had a transient fetal arrhythmia that resolved without antiarrhythmic treatment [16]. Two additional cases were identified in our medical practice and their case descriptions are noted below. Thus a total of three cases were identified that illustrated the key findings pertaining to our systematic review. Fig. 4 illustrates a flow diagram of the studies identified.

3. Case number 1

A 19-year-old primigravid presented in referral at 24 weeks and 6 days during the 2017–2018 influenza seasons with concerns for fetal tachycardia that was noted during a routine anatomy scan performed with her primary obstetri-

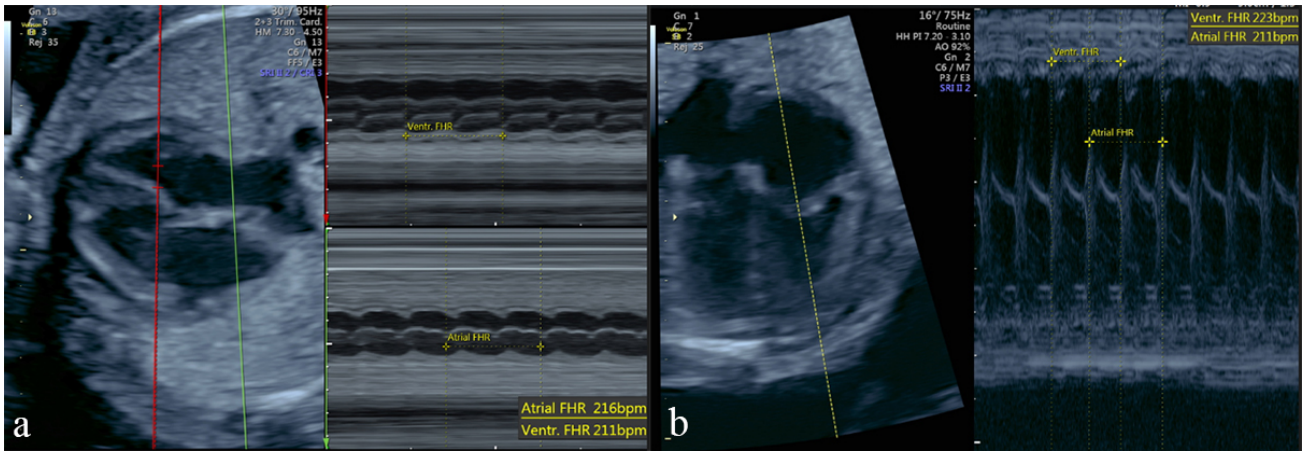

Fig. 1. Fetal supraventricular tachycardia is noted in this fetus. (a,b) The fetal heart rate for the atria range between 211 to 216 beats per minutes, whereas the ventricular heart rate ranges between 211 to 223 beats per minute. In both images, there is a normal 1:1 conduction between the atria and ventricles.

cian. The fetal heart rate was documented to be 200 beats per minute. During the week prior to presentation, she presented with mild symptoms in which she described having a fever; however, of the course of 2–3 days, she began experiencing more moderate symptoms of worsening fatigue and malaise and was diagnosed with influenza at in her local emergency department and prescribed oseltamivir. Of note, she previously declined influenza vaccination.

A comprehensive anatomic assessment was performed including a fetal echocardiogram which noted SVT throughout the examination with 1:1 conduction to the ventricle, with an atrial heart rate between 197–216 bpm, and a ventricular heart rate between 211–250 bpm (Fig. 1a,b). Furthermore, hydrops was diagnosed with pericardial effusion and abdominal ascites (Fig. 2a,b). There was no evidence of structural cardiac disease. No extracardiac anomalies were appreciated and the estimated fetal weight was appropriate for that gestational age. Based on persistent tachyarrhythmia and hydrops, the patient was admitted to the hospital for further evaluation and initiation of transplacental pharmacologic cardioversion.

Influenza polymerase chain reaction (PCR) of nasopharyngeal swab specimen was performed at hospital admission with amplification of Influenza B probe and a treatment course of oseltamivir was started at 75 mg twice daily for 5 days. Maternal symptoms improved and she remained afebrile during her hospital stay.

After normal maternal cardiac evaluation, digoxin was loaded and increased until therapeutic level was reached. As fetal cardioversion was not achieved after 2 days with therapeutic digoxin levels, flecanide was added. Flecainide was titrated to effect and cardioversion occurred with a dose of digoxin 750 mcg daily divided and flecanide 100 mg every 8 hours. Hydrops was resolved by the time of discharge.

Doses of both digoxin and flecanide were gradually decreased secondary to maternal side effects. Recurrent SVT occurred at 27 weeks and she was admitted to the hospital for antiarrhythmic titration. At that time she was started on flecanide mono-therapy at 100 mg every 8 hours with fetal cardioversion. She continued on this regimen until delivery without recurrent arrhythmia.

At 38 weeks and 4 days, she underwent induction of labor secondary to a non-reassuring fetal heart tracing that was noted during the time of a routine non-stress test. She had an uncomplicated vaginal delivery of a male fetus weighing 3045 grams with an APGAR score (appearance, pulse, grimace, activity and respirations) of 8 and one minute and 9 at five minutes of life. Postnatally, a neonatal echocardiogram was performed which noted a normal sinus rhythm and a small patent ductus arteriosus. The newborn was followed closely and found to have episodes of SVT on Holter monitor and pericardial effusion at 6 weeks of life. He was started on atenolol. This was stopped at 8 months of life without recurrent symptoms.

4. Case number 2

A 34-year-old gravida 2 para 1001 presented at 29 weeks and 6 days during the 2019–2020 influenza season with concerns of an abnormal fetal heart rhythm on hand-held Doppler during a routine prenatal visit with her obstetrical provider. The fetal heart rate was reported to be 130 beats per minute but “did not sound normal” per her provider. Three days prior to this visit, she presented with what she initially described as having mild symptoms of an upper respiratory tract infection, to shortly over the course of less than one week, developing more moderate symptoms consisting of worsening fatigue, body aches, malaise and was noted to also be febrile. She presented to her local emergency department for further evaluation and was subsequently diagnosed with influenza infection based on a positive influenza A nasopharyngeal PCR amplification. She was treated with antiviral therapy (oseltamivir) twice

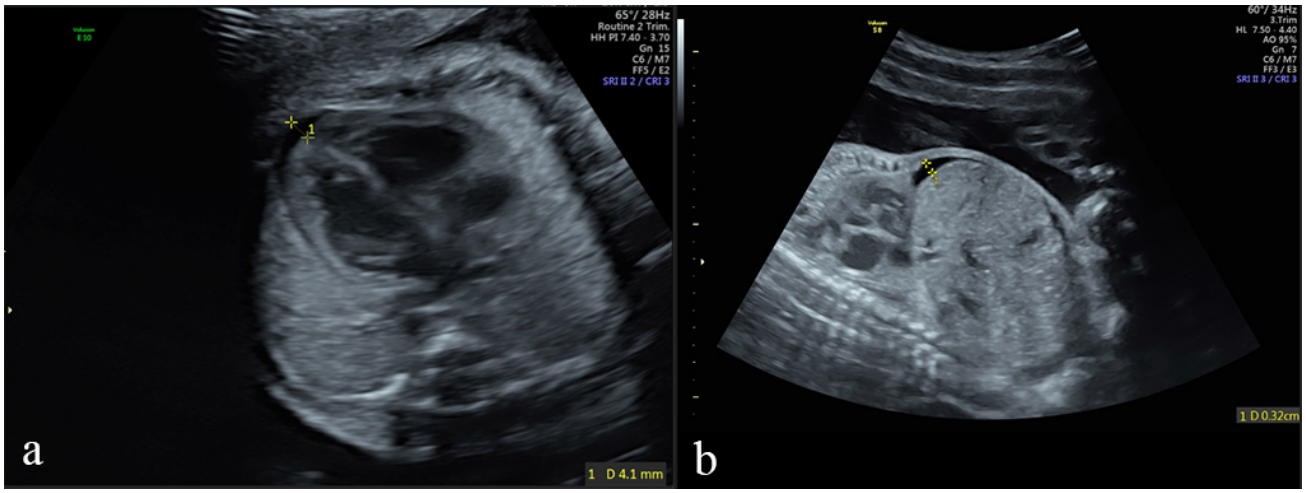

Fig. 2. Hydrops fetalis that occurred secondary to sustained fetal supraventricular tachycardia. (a) Demonstrates evidence of pericardial effusion measuring 4.1 mm in AP diameter. (b) Demonstrates fetal ascites within the abdominal cavity.

daily dosed for the recommended 5-day duration. She previously underwent normal comprehensive anatomic evaluation and fetal echocardiogram secondary to a family history of congenital heart disease. Of note, she previously declined influenza vaccination.

During her initial evaluation, a fetal echocardiogram demonstrated a normal sinus rhythm for a majority of the time with episodes of tachyarrhythmia with the atrial heart rate was as high as 429 beats per minute and the ventricular heart rate was as high as 424 beats per minute. These episodes lasted 10–15 seconds in duration and occurred every 4–5 minutes consistent with an atrial flutter. In addition, there were frequent blocked premature atrial contractions; however, there was a normal 1:1 conduction between the atria and ventricles for the majority of the scan, with short periods or 2:1 conduction between the atria and ventricles (Fig. 3). A small pericardial effusion was identified; however, no evidence of hydrops was noted (Fig. 4). There was no evidence of structural cardiac disease. No extracardiac anomalies were appreciated and the estimated fetal weight was appropriate for that gestational age. At this time, decision was made for expectant management as there was no evidence of sustained tachyarrhythmia or hydrops. From a maternal standpoint, she appeared clinically improved with regards to her influenza viral infection as her malaise, fatigue and body aches improved and she was afebrile.

At 31 weeks and 5 days, the fetus developed persistent atrial flutter with 2:1 atrial to ventricular conduction without hydrops. Given the sustained tachyarrhythmia the decision was made to initiate transplacental antiarrhythmic therapy to achieve cardioversion. After normal maternal cardiac evaluation she was initiated on sotalol 80 mg daily. After fetal cardioversion, she was followed as an outpatient with gradual decrease in dose to 20 mg daily with sustained response.

At 39 weeks and 0 days, she underwent an elective induction of labor and had a normal spontaneous vaginal delivery of a male fetus weighing 3895 grams with an APGAR of 7 at one minute and 9 at five minutes of life. Postnatally, an echocardiogram was performed which noted a normal sinus rhythm and a small patent ductus arteriosus. The newborn was started on digoxin soon after birth. He continued to have non-sustained episodes of supraventricular tachycardia on Holter mentoring at one month of age and continues on digoxin therapy.

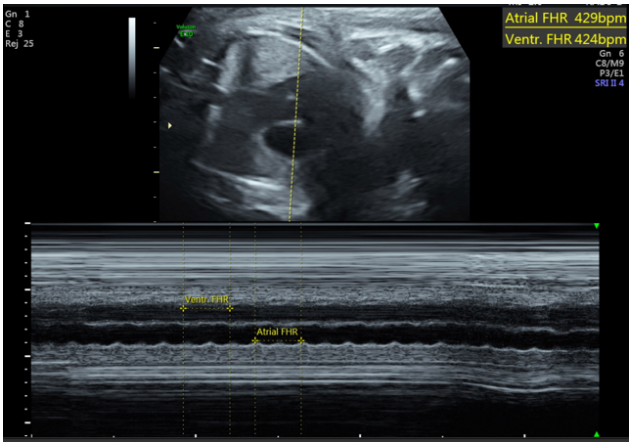

Fig. 3. Fetal atrial flutter is noted in this fetus. The atrial and ventricular heart rates exceed 400 beats per minute. There is a normal 1:1 conduction between the atria and ventricles.

5. Discussion

Based on our systematic review and cases series, a total of three cases have suggested a possible association between fetal arrhythmias and maternal influenza viral infections, thus suggesting that the available literature is scarce. In this article, we presented a case series of two case reports whom were diagnosed with maternal influenza infec-

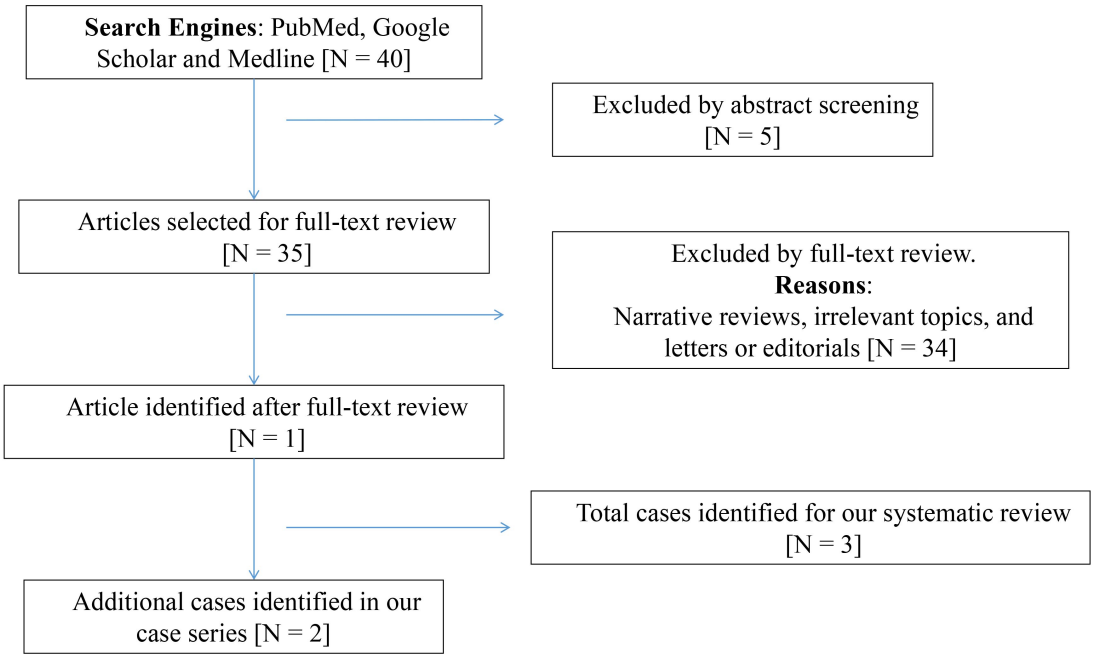

Fig. 4. Selection of articles.

tion during the same flu season, in which fetal tachyarrhythmias were identified. These cases differ from the prior published case report in that for both of our described cases, maternal antiarrhythmic treatment was required to achieve appropriate fetal cardioversion.

Both of the mothers described in this review had confirmed influenza viral infection by PCR amplification. Subtypes were different with both influenza A and B represented. Both patients were treated with oseltamivir antiviral therapy and maternal symptoms improved. With regards to cardiac arrhythmia, oseltamivir can inhibit depolarization currents in animal studies, but the development of arrhythmias have not been previously reported [17,18]. In case 1, fetal arrhythmia developed prior to initiation of oseltamivir. Given these findings, fetal arrhythmia is thought to be secondary to influenza infection as opposed to antiviral therapy.

Non-immune hydrops was noted in our first case report, in which the fetus developed SVT with both pericardial effusion and abdominal ascites; however, the second fetus with atrial flutter had pericardial effusion but had not yet progressed to hydrops. Fortunately, after maternal antiarrhythmic treatment, as well as antiviral treatment, successful cardioversion was achieved and any hydropic findings we reported have resolved. Prior literature has shown that a sustained or prolonged fetal arrhythmia can lead to non-immune hydrops and if not cardioverted in a timely fashion, may lead to high output cardiac failure and ultimately death [19].

Other studies have shown that an accessory pathway is typically involved in cases of fetal SVT, though other forms of conduction abnormalities have been described [20]. Fetal heart rate during SVT typically range between 240–280 beats per min and the management depends on the proportion of time the tachyarrhythmia is present as well as other concerning signs, such as hydrops fetalis [20]. In contrast, atrial flutter typically presents with a fetal heart rate between 300–500 atrial beats per minute and a widely variable ventricular rate dependent on atrioventricular (AV) conduction ratio [20]. Antenatally, the diagnoses of these arrhythmias are established via 2D imaging, by spectral Doppler assessment of the left ventricular inflow and outflow tracts, and by M-mode analysis. With hydrops or sustained arrhythmias, treatment with transplacental antiarrhythmic treatment is recommended to achieve cardioversion [20]. If performed early in the course, hydropic findings may start resolving, allowing not only pregnancy prolongation, but also improving the overall well-being and chance for intact survival for the fetus and neonate [20]. Treatment was initiated early after diagnosis in our two cases with cardioversion resolution of the hydropic changes.

The selection of antiarrhythmic agent to use has been an area of controversy. Recent evidence suggests that digoxin should no longer be considered a first line agent [21]. Table 1 illustrates a list of antiarrhythmic agents that can be considered for the specific type of fetal arrhythmia described. Commonly used antiarrhythmic agents used to treat fetal arrhythmias during pregnancy include digoxin, sotalol, flecainide and amiodarone [20–24]. In

Table 1. Choice of antiarrhythmic treatment for fetal arrhythmias.

Fetal arrhythmia	Treatment considerations
I: Less-serious arrhythmias	
Premature atrial contractions	None
Premature ventricular contractions	None
Atrial bigeminy (conducted or blocked)	None
Non-sustained supraventricular tachycardia	None*
II: More-serious arrhythmias	
Sustained supraventricular tachycardia	• Digoxin • Flecainide • Amiodarone
Atrial flutter	• Digoxin • Sotalol • Propranolol • Amiodarone
Ventricular tachycardia	• Propranolol • Sotalol • Amiodarone • Mexiletine

* Non-prolonged without evidence of fetal hydrops.

our first case, digoxin was unable to achieve cardioversion; whereas, flecanide achieved cardioversion as a single agent. Sotalol was chosen in the second case based on the diagnosis of atrial fibrillation. The two cases described here had fetal arrhythmias that were cardioverted in a timely fashion resulting in a shorter frequency and length of their arrhythmia that was noted on subsequent follow up ultrasound evaluations of their fetal heart.

Based on the findings of this systematic review (three cases in all), we have concluded that as these fetal arrhythmias are often detected during the course of routine prenatal care, we do not feel that any changes with respect to management of maternal influenza infection outside of the routine practice for these women be considered. We believe that this review is clinically important and relevant to medical providers caring for such patients because certain infections, specifically influenza can be associated with adverse pregnancy outcomes and congenital anomalies when acquired early in pregnancy, such as in the first trimester; and these adverse pregnancy outcomes and congenital anomalies are not common later in pregnancy, specifically fetal arrhythmias [25–28]. This is unique to our case series where we described that fetal cardiac disease developed in the second half of pregnancy, of which one patient was in the second trimester, and the second case was in the third trimester, and both cases had arrhythmias. This raises the suspicion that these viral infections, particularly influenza, can lead to adverse pregnancy outcomes at any gestational age; and more so, can certainly be a causative reason for the development of fetal arrhythmias. With that being said, it seems reasonable to assess for concurrent maternal influenza infection in the setting of a fetal arrhythmia identified during pregnancy, should maternal symptoms be present suggesting an influenza infection. With regards to neonatal arrhythmias, arrhythmias are not uncommon; however, the relationship with influenza is scantly published. Currently, there has been evidence noting several abnormalities with electrocardiogram (ECG) monitoring, as well as with cases of myocarditis and myocardial infarction secondary to influenza virus infections [29,30]. These same reports describe cases of regional myocardial dysfunction that was noted in six different patients in which their ECG's noted evidence of myocarditis [30]. Given this scant information, there may in fact be an association between fetal or infantile cardiac arrhythmia and influenza virus infections.

Finally, both patients declined influenza vaccination upon presentation to prenatal care during influenza season. While the ultimate outcome is unknown if influenza vaccination is associated with a reduced risk of a fetus developing an arrhythmia, the risk of maternal influenza infection and subsequent fetal effects, more likely than not, would have been significantly reduced. These cases are instructive examples for fetal benefit of maternal immunization and add further impetus to maternal influenza vaccination efforts to prevent fetal and neonatal morbidity. Lastly, to answer our original research question of whether or not there is a possible association between maternal acquisition of influenza infection during and fetal arrhythmias, though we cannot affirmatively show evidence of a causal link between maternal influenza and fetal arrhythmias, the goal of this systematic review was to identify these cases in hopes that additional cases can be identified; thereby, strengthening an association, and possibly showing a causal link between these two. In addition, we would certainly recommend a larger observational study to evaluate the incidence of fetal arrhythmias in pregnant women infected with influenza. This information is important because it will help answer our question on whether or not there is certainly an association between influenza infection and fetal arrhythmias. Once an association has been established, then additional studies can be conducted to assess if a causal link can be established.

Author contributions

All authors whose names appear on this submission have contributed to the study conception and design. All authors are involved in literary research. Writing manuscript were performed by BHR and JE. Constructing tables were performed by LE. Constructing figures were performed by BR. Material preparation, data collection and analysis were performed by BHR, LE, JE and BR. The first draft of the manuscript was written by BHR and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Informed consent was obtained from all individual participants included in the study to participate and be included in this publication.

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Conflict of interest

The authors declare no conflict of interest. BHR is serving as one of the Guest editors of this journal. We declare that BHR had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MHD.

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