Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

The increase in the rate of maternal deaths related to cardiovascular disease in Japan from 1991–1992 to 2010–2012

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ARTICLE INFO

Article history:
Received 14 July 2015
Received in revised form 30 December 2015
Accepted 10 January 2016
Available online xxx

Keywords:
Pregnancy
Maternal death
Cardiovascular disease

ABSTRACT

Background: Cardiovascular diseases (CVD), both genetic and acquired, increase the risk of maternal death (MD) unless proper genetic/clinical counseling is provided and a multidisciplinary approach is adopted during pregnancy. In recent decades, there has been a significant increase in the number of women with CVD of child-bearing age and in the incidence of pregnancy among relatively older women. However, the impact of this phenomenon on MD has not been carefully investigated.
Methods: This retrospective study compares the incidence and etiology of maternal deaths related to cardiovascular disease (MD-CVD) in Japan in 2010–2012 to that seen in 1991–1992.
Results: Seven cases of MD-CVD were reported in 1991–1992, compared to 15 in 2010–2012. In 2010–2012, the causes included aortic dissection ($n = 5$), peripartum cardiomyopathy ($n = 3$), sudden adult/arrhythmic death syndrome ($n = 2$), acute cardiomyopathy ($n = 2$), pulmonary hypertension ($n = 2$), and myocardial infarction ($n = 1$), and four of these causes were not encountered in 1991–1992. The incidence of MD over the total number of pregnancies decreased from 9.4 per 100,000 cases in 1990–1992 to 4.6 per 100,000 cases in 2010–2012 ($p < 0.05$). However, the incidence of MD-CVD over the number of cases of MD increased from 2.9% in 1991–1992 to 9.7% in 2010–2012 ($p < 0.05$).
Conclusions: The present study demonstrates that the rate of MD-CVD among the cases of MD has increased 3-fold in Japan over the past 20 years. Thus, it is of critical importance to better understand the etiologies and early signs of MD-CVD and to devise an effective management program for pregnancies complicated by CVD.

Introduction

Maternal mortality is widely reported worldwide, despite dramatic advances in the management of pregnancy [1,2]. Most cases involve complications such as postpartum hemorrhage, unsafe abortion, eclampsia, obstructed labor, ectopic pregnancy, embolism, or anesthesia complications during delivery. Nonetheless, nearly 35% of all maternal deaths (MD) are unrelated to the delivery, and the main causes are infection, malaria, anemia, and heart disease.

Pregnant women diagnosed with heart disease currently account for 1% of all pregnant women, which increases to 2–3% when cardiovascular diseases (CVD) such as arrhythmia are included in the cardiac diseases [3,4]. In light of the rising age

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http://dx.doi.org/10.1016/j.jjcc.2016.01.005
0914-5087/

at pregnancy in women and the advances in fertility treatments, an increase in the number of pregnant women with heart disease is expected. This condition is particularly problematic because pregnancy induces an increase in the circulating blood volume and cardiac output due to elevations in ventricular rate and stroke volume. Circulating blood volume increases more rapidly after the 20th week of gestation and plateaus at 40–45% above the normal volume after the 32nd week of gestation [5–7]. Therefore, women with a history of CVD require close management during pregnancy and the following months.

In 2010, the Japanese Circulation Society published the first official 'Guidelines for Indication and Management of Pregnancy and Delivery in Women with Heart Disease' [8]. However, the infrastructure necessary to manage pregnant women with CVD is still lacking, because few studies have documented CVDs in pregnant women. The present retrospective study provides an in-depth analysis of the cases of maternal deaths related to cardiovascular disease (MD-CVD) reported in Japan in 2010–2012, and compares the rates to those seen in a survey conducted in Japan 20 years prior, in 1991–1992 [9–11].

Materials and methods

This retrospective study was conducted on all cases of MD-CVD reported to the Japan Association of Obstetricians and Gynecologists (JAOG) by Japanese healthcare institutions from January 2010 to December 2012 [12]. According to the World Health Organization (WHO), MD is defined as the death of a woman during pregnancy or within 42 days after the end of pregnancy, due to any factor associated to or aggravated by the pregnancy itself or its management, but excluding any accidental or incidental causes. The present study also included cases of late MD, defined as the death of a woman from direct or indirect obstetric causes occurring more than 42 days but less than 12 months after the end of pregnancy. This study was approved by the ethics committee of the National Cerebral and Cardiovascular Center of Japan under the title "Research on a model project regarding surveys and evaluations on maternal mortality in Japan" (receipt number N18-34).

Reporting and review protocols

Since 2010, the clinical information on nearly all cases of MD occurring in Japan has been recorded by the JAOG. When a case of MD occurs, the local medical facility documents each case by using a detailed standard survey that is submitted to the JAOG of each prefecture [13]. Each case is then reviewed by the Maternal Death Exploratory Committee (MDEC), which is chaired by Dr T. Ikeda (principal author of the present manuscript). This committee consists of 15 obstetricians, 4 anesthesiologists, 2 pathologists, and 1 emergency physician. In addition, several specialists attend monthly review sessions to make annual recommendations that aim to reduce the rate of MD in Japan. This study constitutes the first investigation of the characteristics and rates of MD-CVD in Japan that was conducted by the MDEC.

Data collection

The demographic, clinical, and pathological data available on all reported cases of MD-CVD in 2010–2012 were collected from the JAOG database [12,13]. The parameters considered in the analysis were the medical history (excluding CVD), maternal age, parity, type of CVD, time and cause of death, complications during pregnancy, obstetric events, and method of delivery. We also investigated the patients' familial history of connective tissue diseases, including Marfan syndrome. Finally, we assessed the risk factors of peripartum cardiomyopathy in the patients [10,11,14]. The 2010–2012 cases of MD were compared to those documented by Nagaya et al. in Japan in 1991–1992 [9] in terms of mortality rates and the types of CVDs. The rate of MD was defined as the number of all MDs divided by the sum of all live births and fetal deaths, multiplied by 100,000. In the 1991–1992 and 2010–2012 groups, MD-CVD was confirmed by the occurrence of a CVD verified via contrast computed tomography, magnetic resonance imaging, intracardiac electrography, ultrasonography, or autopsy. Several expert obstetricians on the MDEC (2010–2012) or in Nagaya's group (1991–1992) reviewed all the data before confirming CVD as the cause of death. Finally, the duration of CVD was based on the time of presentation of the initial symptoms.

Data analysis

All data are expressed as the number and percentage of cases, and the data were analyzed with Student's *t*-test. Values of $p < 0.05$ were considered statistically significant.

Results

A total of 154 MDs were reported in Japan from January 2010 to December 2012. The cause of MD was CVD in 15 women (9.7%). Among all cases of MD, only five women (8%) died due to obstetric causes occurring more than 42 days but less than 12 months after the end of pregnancy. In two of such late MD cases, the cause of death was CVD. The maternal background, age, and the type of CVD are shown in Table 1. The entire range of child-bearing ages was represented (19–39 years) and the women were mostly primigravida (66.7%). Death occurred during the antepartum (6/15, 40.0%) and the postpartum periods (9/15, 60.0%). Whereas delivery failed in 33.3% of the cases, the mode of delivery for the remaining mothers was vaginal (5/15, 33.3%) or cesarean section (5/15, 33.3%).

The cases of MD-CVD related to aortic dissection were further analyzed with respect to the Stanford classification and family history of connective tissue disease (Table 2). Four cases were classified as type A, whereby the dissection affected the ascending aorta and the arch, rather than sections beyond the brachiocephalic vessels. In case 3, aortic dissection was caused by Marfan syndrome diagnosed before pregnancy. In cases 1 and 2, there was no family history or confirmed diagnosis of Marfan syndrome, but the patients exhibited physical features consistent with the disorder, namely the typical tall and slender build. On the other hand, in cases 4 and 5, the patients did not have familial histories or physical features of Marfan syndrome. However, none of these cases (1, 2, 4, and 5) were autopsied or tested for genetic markers for Marfan syndrome before pregnancy.

Among the cases of aortic dissection, in cases 1, 2, and 4, the first sign of complication was a prodrome of dorsal pain followed by cardiac arrest after 10 h, 1 h 10 min, and 48 h respectively. In case 3, the first sign of complication was epigastric pain after cesarean delivery, and in case 5, the patient developed cardiac arrest without prodromal or any other detectable symptoms.

The deaths of the three patients with CVD involving peripartum cardiomyopathy could not be ascribed to a particular risk factor (Table 3). It is noteworthy that a third of all the 15 patients with MD-CVD died of sudden cardiac arrest. Whereas the patient in case 9 was diagnosed with long QT syndrome, the patient in case 10 had premature ventricular contractions in early pregnancy. The cause of death of both patients was deemed to be sudden adult/arrhythmic death syndrome because there was no known underlying condition to explain the sudden cardiac arrest, other than arrhythmia. Autopsies revealed that in case 11, the patient died of sudden cardiac arrest during treatment for a urinary tract

Please cite this article in press as: Tanaka H, et al. The increase in the rate of maternal deaths related to cardiovascular disease in Japan from 1991–1992 to 2010–2012. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2016.01.005