Maternal and Perinatal Factors Associated With Kawasaki Disease Among Offspring in Taiwan

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Introduction

Kawasaki disease (KD) is the most recognized childhood vasculitis and the leading cause of pediatric-acquired heart disease in developed countries. Increased KD incidence among East Asian children, a high risk among siblings and twins, and familial occurrence suggest a genetic predisposition. However, genetic factors alone cannot explain seasonal variations, periodic outbreaks, or the continued increase in KD incidence. Many other factors, including exposure to infectious agents, pollution, and elevated atmospheric biological particle concentrations, are associated with KD. Several studies have suggested that maternal and perinatal factors might be associated with KD development. This case-control study investigated the role of perinatal factors and maternal autoimmune diseases in the development of KD using the Taiwan Maternal and Child Health Database.

Methods

The institutional review board of the Cathay General Hospital approved this study and waived the need for informed consent because the data are publicly available and deidentified. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for case-control studies.

We collected data of patients who were younger than 5 years, had KD, and were born between 2004 and 2010, from the original claims data of the Taiwan National Health Insurance Research Database, which was established in 1995 and covered 99.9% of the population by 2003. KD diagnosis (International Classification of Diseases, Ninth Revision code 446.1) was confirmed by receipt of intravenous immunoglobulins (Anatomic Therapeutic Chemical code J06BA02) and hospitalization. Age-matched and index date–matched individuals were collected as a control group. Every citizen in Taiwan is assigned a unique national identification number. The Taiwan Maternal and Child Health Database, which contains national identification numbers of children and their parents, was used to link parents and children. The child’s birth history, maternal comorbidities, and maternal autoimmune diseases were analyzed (see the eAppendix in the Supplement).

Differences in categorical and continuous variables were assessed using χ² and t tests, respectively. P values were 2-sided, and statistical significance was set at P < .05. Analyses were performed using SAS Enterprise Guide statistical software version 9.4 (SAS Institute). The analyses were conducted from May 1 to August 6, 2020.

Results

We enrolled 4197 patients with KD (2601 boys [62.0%]; 1717 [40.9%] younger than 1 year; 1261 [30.0%] aged 1 year) and 16788 matched individuals without KD (8832 boys [52.6%]) from 1280374 children in the database. Male sex (odds ratio [OR], 1.47; 95% CI, 1.37-1.57; P < .001), maternal age 35 years or older (OR, 1.18; 95% CI, 1.07-1.30; P < .001), maternal age 35 years or older (OR, 1.18; 95% CI, 1.07-1.30; P < .001), maternal Sjögren syndrome (OR, 1.75; 95% CI, 1.03-2.95; P = .04), and maternal ankylosing spondylitis (OR, 2.01; 95% CI, 1.69-2.39; P = .05) were associated with KD.
were associated with increased KD risk in the offspring. However, low birth weight, preterm delivery, other maternal autoimmune diseases, and maternal comorbidities showed no associations with risk of developing KD (Table 1). In the multivariable analysis, maternal ankylosing spondylitis was associated with a 2.02 times higher odds of KD in the offspring (95% CI, 1.18-3.47; \( P = .01 \)) (Table 2).

### Table 2. Multivariable Analysis of Autoimmune Diseases Associated With Kawasaki Disease

| Autoimmune disease                      | Model 1\(^a\) | Model 2\(^b\) |
|-----------------------------------------|---------------|---------------|
|                                         | OR (95% CI)   | \( P \) value | OR (95% CI)   | \( P \) value |
| Systemic lupus erythematosus            | 0.85 (0.43-1.67) | .63          | 0.86 (0.43-1.71) | .67          |
| Rheumatoid arthritis                    | 0.78 (0.41-1.49) | .45          | 0.79 (0.41-1.52) | .49          |
| Sjögren syndrome                        | 1.74 (1.03-2.94) | .04          | 1.67 (0.99-2.84) | .06          |
| Ankylosing spondylitis                  | 1.97 (1.15-3.37) | .01          | 2.02 (1.18-3.47) | .01          |
| Psoriatic arthritis or psoriasis        | 0.85 (0.41-1.74) | .65          | 0.85 (0.41-1.74) | .65          |
| Autoimmune thyroiditis                  | 1.38 (0.65-2.94) | .41          | 1.40 (0.65-2.99) | .39          |

Abbreviation: OR, odds ratio.

\(^a\) Model 1 was adjusted for neonatal sex and maternal age.

\(^b\) Model 2 was adjusted for neonatal sex, maternal age, neonatal age, birth weight, preterm delivery, and maternal comorbidity.

### Table 1. Characteristics of Study Participants and Factors Associated With KD

| Characteristic                  | Non-KD group (\( n = 16\,788 \)) | KD group (\( n = 4197 \)) | OR (95% CI)   | \( P \) value |
|---------------------------------|----------------------------------|---------------------------|---------------|--------------|
| Age, y                          | 6868 (40.9)                      | 1717 (40.9)               | NA\(^a\)      | NA\(^a\)     |
| 0                               | 5044 (30.0)                      | 1261 (30.0)               |               |              |
| 2                               | 2336 (13.9)                      | 584 (13.9)                |               |              |
| 3                               | 1180 (7.0)                       | 295 (7.0)                 |               |              |
| 4                               | 824 (4.9)                        | 206 (4.9)                 |               |              |
| 5                               | 536 (3.2)                        | 134 (3.2)                 |               |              |
| Sex                             | 7956 (47.4)                      | 1596 (38.0)               | 1 [Reference] | <.001        |
| Female                          | 8832 (52.6)                      | 2601 (62.0)               | 1.47 (1.37-1.57) | <.001        |
| Male                            |                                  |                           |               |              |
| Birth weight, g                 | 15 672 (93.4)                    | 3929 (93.6)               | 1 [Reference] | <.001        |
| ≥2500                           | 1116 (6.6)                       | 268 (6.4)                 | 0.96 (0.84-1.10) | .55          |
| <2500                           |                                  |                           |               |              |
| Mother’s age, y                 | 14 611 (87.0)                    | 3571 (85.1)               | 1 [Reference] | <.001        |
| <35                             | 2177 (13.0)                      | 626 (14.9)                | 1.18 (1.07-1.30) | <.001        |
| ≥35                             |                                  |                           |               |              |
| Preterm delivery, wk            | 15 448 (92.0)                    | 3856 (91.9)               | 1 [Reference] | <.001        |
| ≥37                             | 1340 (8.0)                       | 341 (8.1)                 | 1.02 (0.90-1.15) | .76          |
| <37                             |                                  |                           |               |              |
| Maternal comorbidity            |                                  |                           |               |              |
| Diabetes                        | 125 (0.7)                        | 27 (0.6)                  | 0.86 (0.57-1.31) | .49          |
| Hypertension                    | 143 (0.9)                        | 39 (0.9)                  | 1.09 (0.77-1.56) | .63          |
| Hyperlipidemia                  | 202 (1.2)                        | 54 (1.3)                  | 1.07 (0.79-1.45) | .65          |
| Gestational diabetes            | 272 (1.6)                        | 60 (1.4)                  | 0.88 (0.67-1.17) | .38          |
| Gestational hypertension        | 84 (0.5)                         | 23 (0.5)                  | 1.10 (0.69-1.74) | .70          |
| Preeclampsia or eclampsia       | 188 (1.1)                        | 51 (1.2)                  | 1.09 (0.80-1.48) | .60          |
| Maternal autoimmune disease     |                                  |                           |               |              |
| Systemic lupus erythematosus    | 47 (0.3)                         | 10 (0.2)                  | 0.85 (0.43-1.69) | .64          |
| Rheumatoid arthritis            | 55 (0.3)                         | 11 (0.3)                  | 0.80 (0.42-1.53) | .50          |
| Sjögren syndrome                | 46 (0.3)                         | 20 (0.5)                  | 1.75 (1.03-2.95) | .04          |
| Ankylosing spondylitis          | 40 (0.2)                         | 20 (0.5)                  | 2.01 (1.17-3.43) | .01          |
| Psoriatic arthritis or psoriasis| 43 (0.3)                         | 9 (0.2)                   | 0.84 (0.41-1.72) | .63          |
| Autoimmune thyroiditis          | 26 (0.2)                         | 9 (0.2)                   | 1.39 (0.65-2.96) | .40          |

Abbreviations: KD, Kawasaki Disease; NA, not applicable; OR, odds ratio.

\(^a\) The groups were age matched so no comparisons were made.
Discussion

Given that the age of KD onset is between 6 months and 5 years, and it is most severe during the first year of life, it is possible that the child’s immature immune system and maternal and perinatal factors might be associated with KD development. However, the identification of maternal associations, especially when investigating perinatal factors associated with pediatric diseases, is the challenge when integrating different large databases to link maternal health information with the child’s clinical phenotypes. In this study, we found that advanced maternal age was significantly associated with KD development in the offspring. This association may partly explain the increasing KD incidence in developed countries because ages at marriage and childbearing are increasing. The advanced parental age may be associated with more germline de novo variants, which may lead to KD in the offspring. Furthermore, we demonstrated that maternal ankylosing spondylitis and Sjögren syndrome may be perinatal factors associated with increased risk of KD. This suggests that a maternal autoimmune disease or its associated medical treatment might induce an epigenetic predisposition to developing KD in the offspring.

The main limitation of the study was the unavailability of the genetic and environmental confounders. Moreover, our findings are based on data of patients who were younger than 5 years. Therefore, the role of maternal factors in increasing the risk of KD in offspring requires further investigation, especially in older patients.

ARTICLE INFORMATION

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Author Contributions: Dr C.-H. Lin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPLEMENT.

eAppendix. Supplemental Methods