BACKGROUND: Peripartum cardiomyopathy (PPCM) is a rare disorder associated with pregnancy that can lead to life-threatening conditions. The incidence and clinical characteristics of this condition remain poorly understood.

METHODS AND RESULTS: We aimed to perform the first population-based study of PPCM in South Korea, using the Korea National Health Insurance Claims Database of the Health Insurance Review and Assessment Service. Patients who fulfilled predefined diagnostic criteria for PPCM from January 1, 2010, to December 31, 2012, were identified from International Classification of Diseases, Tenth Revision, Clinical Modification codes. To discriminate PPCM from other causes of heart failure, we excluded subjects who already had heart failure-related International Classification of Diseases, Tenth Revision, Clinical Modification codes at least 1 year before delivery. During the study period, there were 1 404 551 deliveries in South Korea, and we excluded 20 159 patients who already had heart failure. In those, a total of 795 cases were identified as PPCM. Patients with PPCM were older, had a higher prevalence of preeclampsia and gestational diabetes mellitus, and were more likely to be primiparous and have multiple pregnancies. Moreover, cesarean section and pregnancy-related complications and in-hospital death were also more common in patients with PPCM. Intriguingly, a considerable number of heart failure cases (n=64; 8.1% of total PPCM) were noted between 5 and 12 months after delivery.

CONCLUSIONS: The incidence of PPCM was 1 in 1741 deliveries in South Korea. Patients with PPCM were older, were more associated with primiparity and multiple pregnancy, had more pregnancy-related complications, and revealed higher in-hospital mortality than controls. The number of cases diagnosed as PPCM were decreased over time after delivery; however, a large number of patients were still noted through 12 months after delivery.
Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy associated with pregnancy, which represents a life-threatening condition. The incidence and clinical profile of this condition remain poorly understood because of its rarity, uncertain definition, and geographical differences.1 Moreover, there are no large population-based studies on the incidence and clinical characteristics of PPCM in South Korea. The previous PPCM criteria, which was established in 1971, limited the time frame of PPCM between 1 month antepartum and 5 months postpartum; however, numerous later publications have described earlier or later development of cardiomyopathy during pregnancy.3,4 According to concern about time-related cutoffs of PPCM definition could lead to underdiagnosis of PPCM, the definition has been revised in 2010 by Heart Failure Association of the European Society of Cardiology Working Group on PPCM and defined as an idiopathic pregnancy-associated heart failure (HF) that develops toward the end of pregnancy or in the following months after delivery in a woman without previously known structural heart disease.4

The incidence of PPCM varies widely and depends on ethnic and geographical differences, which ranges from 1:300 in Haiti to 1:4000 in the United States.5–7 Differences in incidence among the previous studies might be because of variations in estimating method; however, limited data are available to address this issue. Moreover, only a few data are available regarding the incidence of PPCM in Asian populations.8 Currently, strong risk factors for PPCM include advanced age, black race, preeclampsia, hypertension, multiple gestations, anemia, and prolonged tocolysis.9 Nonetheless, most of preeclampsia women do not manifest as PPCM, and a large proportion of patients with PPCM is young primiparous women.10 These findings suggest that the process of disease is heterogeneous and seems to have diverse phenotypic variations according to its genetic backgrounds, geographical backgrounds, and environmental factors. Hence, determination of risk factors for PPCM in South Korea would be important for identification of those at higher risk. A nationwide epidemiological study may clarify the incidence and risk factors for PPCM in Korean population and can be used to determine appropriate clinical guidelines specific to this population.

Therefore, we aimed to perform the first large population-based study of the incidence of PPCM in South Korea and to determine characteristics, risk factors, and short-term mortality for PPCM. In addition, we examined the time of diagnosis of cardiomyopathy based on our data.

MATERIALS AND METHODS

Data Source

We collected the data from the Korea National Health Insurance Claims Database of the Health Insurance Review and Assessment Service from 2009 to 2013. In Korea, the Korea National Health Insurance is the largest all-payer hospitalization database, and enrollment is mandatory for all Koreans. The Korea National Health Insurance provides universal health insurance for almost all Koreans (97%), and the remaining 3% of the population is covered by a Medical Aid Program. The data set of Health Insurance Review and Assessment Service includes disease codes registered by clinicians and stratified according to the International Classification of Diseases, Tenth Revision, Clinical Modification, as well as demographic information, treatments, surgical procedures, and prescribed medicines; prescription dates and medical costs are also recorded. This study was approved by the Institutional Review Boards of the Korea University Guro Hospital (institutional review board No. 17096-001).

Case Identification

The database received from Health Insurance Review and Assessment Service consisted of deidentified codes representing each individual, together with age, sex, diagnosis, and a list of prescribed procedure-related codes. With this database, we used International Classification of Diseases, Tenth Revision, Clinical Modification diagnosis and procedure codes to identify all women who gave birth during the study period. Within this cohort, we investigated possible cases of
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Peripartum Cardiomyopathy (PPCM) from 1 month antepartum to 5 months postpartum by using not only PPCM code itself but performed a search based on HF-related International Classification of Diseases, Tenth Revision, Clinical Modification codes (Table 1). We applied this method because using PPCM codes alone for patient screening could miss some cases that were not properly coded. Because patients require a prescription from a clinician at least every year to refill medication in Korea, we hypothesized that those who already had HF before the study period might have medical records (with diagnosis or prescription codes for HF) that preceded study enrollment. Hence, to differentiate PPCM from other causes of HF and to prevent overestimation, we excluded all patients who already had HF-related International Classification of Diseases, Tenth Revision, Clinical Modification codes or any claims for HF-related medications a year before delivery and performed an investigation from January 1, 2010, to December 31, 2012 (Figure 1; Table I in the Data Supplement). For example, a patient who was diagnosed with HF in 2009, or a patient with a record of a prescription for HF, such as diuretics, was considered to have HF and was excluded from the analysis. Furthermore, to avoid chance of exclusion of female subjects with preexisting hypertension, we considered only diuretics who are receiving prescription at least ≥2 which are usually prescribed in acute symptomatic HF (such as furosemide and spironolactone, not thiazide). See Table I in the Data Supplement for detailed information about excluded cases. We used age 35 years as a cutoff value to define older maternal age, which is a commonly accepted definition of advanced maternal age in Korea. We also examined data on parity status (primiparous: given birth for the first time), multiple pregnancies (a pregnancy of ≥2 fetuses), delivery mode (vaginal delivery or cesarean section), and presence of pre eclampsia to identify risk factors related to PPCM. In addition, to analyze clinical characteristics, risk factors, and short-term mortality for PPCM, patients with PPCM were compared with control group (n=1,383,654), who had a delivery without a mortality for PPCM, patients with PPCM were compared to analyze clinical characteristics, risk factors, and short-term analysis. Furthermore, to avoid chance of exclusion of female subjects with preexisting hypertension, we considered only diuretics who are receiving prescription at least ≥2 which are usually prescribed in acute symptomatic HF (such as furosemide and spironolactone, not thiazide). See Table I in the Data Supplement for detailed information about excluded cases. We used age 35 years as a cutoff value to define older maternal age, which is a commonly accepted definition of advanced maternal age in Korea. We also examined data on parity status (primiparous: given birth for the first time), multiple pregnancies (a pregnancy of ≥2 fetuses), delivery mode (vaginal delivery or cesarean section), and presence of pre eclampsia to identify risk factors related to PPCM. In addition, to analyze clinical characteristics, risk factors, and short-term mortality for PPCM, patients with PPCM were compared with control group (n=1,383,654), who had a delivery without a diagnosis of PPCM from 2010 to 2012.

Statistical Analysis

Patients with PPCM were compared with control cohorts, and the crude incidence was calculated as the ratio of the number of deliveries with PPCM to the total number of deliveries in the database. Continuous variables were presented as mean±SD and categorical variables as percentages. Comparisons between groups were performed by using the t test for continuous variables and χ2 test for categorical values in univariate analysis. The odds ratios (ORs) for PPCM and corresponding confidence interval (CI) associated with demographics and comorbid conditions were determined by using univariate or multivariate logistic regression models. Demographic factors (such as older age, primiparity, and multiple pregnancy), clinical factors (such as preeclampsia and gestational diabetes mellitus [DM]), delivery factors (cesarean delivery, induction labor, and instrumental delivery), and maternal complications (placenta previa, placenta abruption, uterine arterial embolization, and peripartum hysterectomy) were included in the model as potential predictors. All analyses were conducted with SPSS software, version 12.0 (SPSS, Inc, Chicago, IL). A P value <0.05 was considered statistically significant. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

RESULTS

Baseline Characteristics and Risk Factors

After excluding 20,102 patients of preceding probable HF, there were 1,384,449 deliveries in South Korea from 2010 to 2012 (Table 2). Among these, 795 cases had codes that we defined as PPCM. Thus, the overall rate of PPCM was 1 in 1,741 (95% CI, 1,654–1,829) deliveries in South Korea. The mean age was 32.1±4.3 years in the PPCM group and 30.9±4.1 years in the control group (P<0.001); older women (≥35 years) were more common in PPCM group than in controls (29% versus 18%; P<0.001). Moreover, when divided into 4 groups based on age, older age was linearly associated with increasing prevalence of PPCM (P for trend, <0.001; Table II in the Data Supplement). The multivariate adjusted ORs were 1.00, 1.25, 1.78, and 1.96, respectively, for PPCM according to age in the 1st, 2nd, 3rd, and 4th groups (P for trend, <0.001; Table II in the Data Supplement). The PPCM group was more likely to be primiparous (P=0.033) and have multiple pregnancies (P<0.001) than the control group. In addition, cesarean section, preeclampsia, and gestational DM were more common in the PPCM group (P<0.001 for all). Induction of labor (P<0.001) and instrumental delivery (P=0.023), which are normal spontaneous delivery-related procedures, were more common in the control group. Pregnancy-related complications, such as placenta previa (P=0.026), placenta abruption (P<0.001), uterine arterial embolization (P<0.001), and peripartum hysterectomy (P<0.001), were more prevalent in the PPCM group.

Patient Risk Factors Associated With PPCM

Baseline risk factors in the PPCM group were compared with those in the control group using logistic

<table>
<thead>
<tr>
<th>ICD-10-CM</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I90.3</td>
<td>Cardiomyopathy in the puerperium</td>
</tr>
<tr>
<td>I42.8</td>
<td>Other cardiomyopathies</td>
</tr>
<tr>
<td>I42.9</td>
<td>Cardiomyopathy, unspecified</td>
</tr>
<tr>
<td>I50.1</td>
<td>Left ventricular failure</td>
</tr>
<tr>
<td>I50.2</td>
<td>Systolic (congestive) HF</td>
</tr>
<tr>
<td>I50.4</td>
<td>Combined systolic (congestive) and diastolic (congestive) HF</td>
</tr>
<tr>
<td>I50.9</td>
<td>HF, unspecified</td>
</tr>
</tbody>
</table>

HF indicates heart failure; and ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.
regression. Multivariate analysis ORs for PPCM associated with all baseline factors are shown in Table 3. Age ≥35 years (OR, 1.56; 95% CI, 1.32–1.83), primiparity (OR, 1.18; 95% CI, 1.02–1.37), multiple pregnancy (OR, 2.19; 95% CI, 1.64–2.93), cesarean section (OR, 2.59; 95% CI, 2.15–3.14), preeclampsia (OR, 6.02; 95% CI, 4.94–7.34), and gestational DM (OR, 1.70; 95% CI, 1.26–2.29) were significantly correlated with PPCM in multivariate analysis. The risks of postpartum complications, such as uterine arterial embolization (OR, 5.24; 95% CI, 2.88–9.56), and peripartum hysterectomy (OR, 8.30; 95% CI, 4.84–14.22) were markedly increased in patients with PPCM. However, induction of labor, instrumental delivery, and placenta previa were not significantly increased in the PPCM group when compared with the control group. Intriguingly, the rate of PPCM was exponentially increased when each additional risk factor associated with PPCM was added and was ≈200× greater in patients with ≥6 risk factors than in those with none (Figure 2).

### In-Hospital Mortality

We investigated in-hospital mortality by using the hospitalization claim data incorporating the individual cases of PPCM, and we could analyze the cases classified as death by the medical treatment code. During 2010 to 2012, in-hospital death was reported in 8 cases in PPCM group (4 patients died <3 days after admission and 6, 9, 13, and 25 days in 1 patient each after admission) and 197 cases in control group. Crude in-hospital mortality was significantly higher in PPCM group than in controls (1.00% versus 0.01%; *P*<0.001).

### Time of Diagnosis of PPCM

Time of diagnosis (Figure 3) with PPCM was determined before delivery in 383 patients (48%) and after delivery in 412 patients (52%). Among patients with PPCM diagnosed after delivery, the majority (n=190; 46%) were diagnosed during the first postpartum week; an additional 25% (n=103) were diagnosed between 1 week and 1 month postpartum. Between 1 and 5 months postpartum, there was a marked decrease in diagnoses; 119 patients with PPCM (29%) were diagnosed 2 to 5 months after delivery, with 57 (14%) in the second month, 23 (6%) in the third month, 24 (6%) in the fourth month, and 15 (4%) in the fifth month. Intriguingly, when we extended the diagnosis of the HF period to 1 year, a considerable number of patients were still diagnosed with PPCM, as noted in Figure 3 (n=64; 8.1% of the total and 16% of postpartum PPCM cases).

### DISCUSSION

In this nationwide, large community-based cohort in South Korea, 1 in 1741 (95% CI, 1654–1829) delivered pregnancies developed PPCM, as defined by our study protocol. The incidence rates were considerably higher in an older population. Patients with PPCM had a higher prevalence of preeclampsia and gestational DM and were more likely to be primiparous and have multiple pregnancies than controls. In addition, not only was cesarean section more common during deliv-
ery but related complications were also more common (placenta abruption, uterine arterial embolization, and peripartum hysterectomy) in patients with PPCM. The in-hospital mortality of PPCM was more common than control. Interestingly, a considerable number of patients with HF were still observed ≤12 months after delivery.

During the study period, the overall incidence of PPCM was 1 in 1741 (95% CI, 1654–1829) deliveries. This is consistent with previously reported estimates of incidence, ranging from 1 in 300 to 1 in 4000 deliveries.5,6 A recent inpatient code-based analysis of 64 million discharge hospital records from the United States reported 34,219 cases of PPCM, with an incidence of 1 in 968 births.11 In that study, both the incidence and mean age of the overall cohort (30.3 versus 30.9 years) were similar to those in our study, suggesting that our estimates were credible. On the other hand, a population-based study reported an estimated incidence of PPCM in Japan of 1 in 20,000 deliveries.8 The study was based on a questionnaire survey and could have been influenced by selection or recall bias and also might have underestimated PPCM incidence because of undiagnosed or missed patients. In addition, most previous estimates were not population based (most were based on case series or reviews of the literature).12–14 Hence, we think that our estimate more closely reflects the true incidence of PPCM.

Our study used multivariable statistical modeling to identify independent risk factors for PPCM, and we confirmed associations between previously identified risk factors. Comorbidities correlated with PPCM, such as older maternal age,15,16 and preeclampsia17 were significantly associated with PPCM in our study as well. Our study demonstrated that preeclampsia confers a >6-fold increased risk of developing PPCM—a magnitude of effect similar to that in a previous report (4-fold increased risk of PPCM).17 Numerous studies have shown that preeclampsia is an established risk factor for PPCM and may share pathogenesis with PPCM.8,17,18 In fact, an antian- giogenic factor (soluble fms-like tyrosine kinase-1), which has been identified in placental secretions, is elevated in preeclampsia and can cause cardiac dysfunction.18,19 Levels of soluble fms-like tyrosine kinase-1 are increased in a subset of patients with PPCM, and this pathophysiological overlap may, partly, explain the higher prevalence of concurrent preeclampsia in women diagnosed with PPCM. To unravel the pathognomonic role of soluble fms-like tyrosine kinase-1 in PPCM and in preeclampsia, future study is warranted by measuring the levels of soluble fms-like tyrosine kinase-1 in such subjects.

Moreover, our study expands on the existing knowledge of risk factors for PPCM by identifying gestational DM as an important predictor. A population-based survey in the United States reported that the prevalence of gestational DM in Asian women was twice than non-Hispanic white women,20 which reflects the importance of gestational DM as a risk factor for PPCM in Asian populations. To our knowledge, this is the first report to demonstrate a strong independent link between gestational DM and PPCM. Previous report that an increase in cleaved prolactin triggers endothelial and cardiomyocyte damage could be a possible explanation for the association between gestational DM and PPCM; however, it has been only proven in the animal model.21 A potential mechanism between gestational DM and PPCM may include
shared pathogenesis between the diabetic cardiomyopathy and the PPCM, which involves angiogenic imbalance owing to downregulation of proangiogenic factors, such as VEGF (vascular endothelial growth factor).18,22

Multiparity and multiple pregnancy have traditionally been considered risk factors for PPCM.10,17 In contrast with prior literature, our study showed that primiparity was a greater risk factor for PPCM. Most previous studies documented the development of PPCM in association with the first or second pregnancy in more than half of patients.23,24 Therefore, there are limited data to support an association between multiparity and PPCM. Meanwhile, a recent study clearly reported that women diagnosed with PPCM had a significantly higher proportion of primiparity and multiple pregnancy,25 which strengthens the results of our study.

In our study, high rates of cesarean delivery and pregnancy-related complications, such as placenta abrupti-
on, uterine arterial embolization, and peripartum hysterectomy, were documented in patients with PPCM. The higher rate of cesarean delivery may reflect the higher incidence of older maternal age, multiple pregnancy, and preeclampsia. Early labor or cesarean delivery itself might contribute to the development of PPCM; however, we think that cesarean delivery is more likely to occur in women with symptomatic HF in PPCM. To clarify, we analyzed a point of time between diagnosed as PPCM and cesarean section. Among the 795 PPCM subjects, cesarean section was done in 513 (64.5%) patients. In these, most of patients with PPCM were diagnosed as PPCM before undergoing a cesarean section (n=320; 62.4%), and the other patients with PPCM were diagnosed as PPCM after a cesarean delivery (n=193; 37.6%). These findings strongly suggest that the PPCM is responsible for cesarean section but not cesarean section per se is attributed to occurrence of PPCM in delivery patients. Placenta abruption, uterine arterial embolization, and peripartum hysterectomy are associated with blood loss in delivery. In these situations, massive transfusion or fluid resuscitation are usually required, and these conditions may induce HF at the time of delivery. Therefore, it is not surprising that we observed an increase in conditions associated with peripartum hemorrhage in patients with PPCM.

The in-hospital mortality of patients with PPCM was higher than normal delivering mothers (1.00% versus 0.01%; P<0.001). This finding is consistent with the recently published in-hospital mortality rate of 1.30% to 1.36% in PPCM1,2 and less than previously reported in-hospital mortality rate of 2.05% in PPCM. Increased level of awareness of PPCM, coupled with advanced HF management, may have positively influenced on this rare disease.

In study, by using the timing of PPCM defined by Demakis et al., we identified 795 patients with PPCM, and the majority (n=573; 72.1%) were diagnosed between 1 month before delivery and the first postpartum week, which is a consistent finding with the result of Demakis et al. Moreover, when we searched for patients with diagnosis codes for HF for ≤1 year after delivery, a considerable number was identified. The working group on PPCM of the European Society of Cardiology recently revised the definition of PPCM, in which deleted the strict time cutoff. Our findings agree on this revised definition and strengthen the concept that patients with HF diagnosed ≥5 months after delivery reflect presentations of the same condition at different times.

Limitations

Our study had some limitations. First, given the observational nature of our study, the relationship between causes of PPCM and the effect of risk factors is difficult to determine. Second, insufficient coding or diagnostic code misclassification could have led to overestimation or underestimation of PPCM cases. However, in our study protocol, we extensively reviewed at least 1 year of prior claims data to exclude preexisting probable HF in the calculation of PPCM incidence, which could result in reasonable incidence rates of PPCM in South Korea. Moreover, our results were similar to those of other reports regarding incidence and known risk factors for PPCM. In addition, we excluded the cases which were previously prescribed for HF medications, and this could potentially overestimate the incidence of PPCM. However, excluded numbers by claimed medications were only 13.2% (n=2660) of total excluded cases (Table I in the Data Supplement), and also we limited the medications for exclusion to usually prescribed diuretics for symptomatic HF (furosemide and spironolactone) not for hypertension (thiazide). Therefore, some patients with mild HF who used thiazide for HF management could be missed. Third, owing to the nature of Korea National Health Insurance system (only covers 97% of Korean population), there is a 3% chance of occurring error when based on our database. Fourth, individual patient analysis was impossible because the Health Insurance Review and Assessment Service data were deidentified, and echocardiographic parameters, including left ventricular ejection fraction, left ventricular size, presence of left ventricular thrombus, which were identified as predictors of adverse outcomes for PPCM, were not available. Fifth, our data were only derived from in-hospital records at the time of delivery; therefore, we were unable to examine the long-term adverse events of PPCM. Furthermore, we might have missed a certain number of undetected PPCM patients who have milder forms of heart failure. To solve these issues, further prospective research is needed. Finally, we could not determine whether any records represented the same patient with multiple deliveries. Patients with PPCM are often advised against subsequent pregnancies because of concern about worsening HF and adverse outcomes; therefore, patients with PPCM likely represented only a minority of those with subsequent pregnancies.

Conclusions

In South Korea, the incidence of PPCM was 1 in 1741 (95% CI, 1654–1829) deliveries. Women with PPCM were older, more likely to have primiparity and multiple pregnancies, and had more pregnancy-related complications than controls. Moreover, pregnant women having additional risk factors are more likely to experience PPCM than subjects who have fewer risk factors. Patients with PPCM have high in-hospital mortality rate than normal delivery subjects. Most of patients with
PPCM were documented in the last month of pregnancy or within the first month after delivery; however, still a considerable number of patients with newly developed HF were noted through 1 year after delivery.

ARTICLE INFORMATION
Received April 12, 2017; accepted February 26, 2018.

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Sources of Funding
This study was supported by a grant of the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (grant no. H16C0483).

Disclosures
None.

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