

# Possible effects of anaesthetic management on the 1 yr followed-up risk of herpes zoster after Caesarean deliveries

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## Editor's key points

- General anaesthesia may impair immune function.
- This population registry study investigated the 1 yr incidence of herpes zoster after Caesarean section (CS).
- The incidence of herpes zoster was greater after CS under general anaesthesia compared with regional anaesthesia.
- More data are needed to confirm these findings.

**Background.** As general anaesthesia may compromise the immune system, it has been hypothesized that latent varicella-zoster virus is more likely to be reactivated and cause herpes zoster in mothers after Caesarean deliveries under general anaesthesia. Our study was thus aimed at investigating the risk of herpes zoster among women during the first year after Caesarean deliveries under either general or regional anaesthesia.

**Methods.** Two nationwide population-based data sets were utilized, including the Taiwan birth certificate registry and the Taiwan National Health Insurance Research Dataset. From 2001 to 2003, a total of 162 495 women underwent Caesarean delivery. Among them, 21 454 women received general anaesthesia, whereas 141 041 patients received regional anaesthesia. Each individual was followed for 1 yr to identify the subsequent occurrence of herpes zoster. Cox's proportional hazards regressions were performed for analysis.

**Results.** During the 1 yr follow-up period, 0.46% of the women receiving general anaesthesia experienced an episode of herpes zoster, compared with 0.34% of women receiving regional anaesthesia. In Caesarean deliveries, the use of general anaesthesia compared with regional anaesthesia was independently associated with a 1.29-fold (95% confidence interval=1.04–1.61) increase in the 1 yr risk of herpes zoster, after adjusting for maternal and infant characteristics.

**Conclusions.** In this series, there was a small increased risk of herpes zoster in the year after Caesarean delivery with general anaesthesia. Future studies are needed to further investigate these findings.

**Keywords:** anaesthesia, general; anaesthesia, regional; Caesarean section; herpes zoster; immunity

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Regional and general anaesthesia are commonly used for Caesarean deliveries.<sup>1</sup> Compared with general anaesthesia, women receiving regional anaesthesia (either spinal or epidural) have been reported to have a lower estimated blood loss.<sup>2</sup> No significant difference has been identified in terms of major maternal or neonatal outcomes between these two groups of women undergoing Caesarean section (CS).<sup>2</sup> Nevertheless, little is known about the difference in long-term consequences on maternal health outcomes between these two modes of anaesthesia.

Preliminary findings suggested that general anaesthesia decreases immunological function.<sup>3</sup> Herpes zoster, which more frequently attacks people with impaired immune systems, is a neurocutaneous disease stemming from the varicella-zoster virus (VZV). The initial infection with VZV often occurs in children and young people and causes the acute disease of chickenpox. Once an episode of chickenpox

has been resolved, VZV is not eliminated but remains dormant in the dorsal root and cranial nerve ganglia. As VZV-specific cellular immunity declines with time, the virus can later be reactivated to cause herpes zoster.<sup>4</sup>

The annual incidence rate of herpes zoster worldwide is ~1.2–3.4 cases per 1000 persons.<sup>5–7</sup> In addition to cutaneous complications, it can cause nervous system complications and can impair quality of life. Therefore, it is of clinical and public health concern.

As general anaesthesia may compromise the immune system,<sup>3</sup> we speculated that previously latent VZV is more likely to be reactivated in mothers after CS under general anaesthesia. Thus, the aim of this study was to investigate the risk of herpes zoster in women during the year after CS. The 1 yr follow-up period was chosen because caring for infants from birth to 1 yr old is physically and psychologically demanding and may affect maternal health. It was

hypothesized that the risk of herpes zoster would be greater for women receiving general anaesthesia than those receiving spinal/epidural anaesthesia.

## Methods

### Database

This study used two nationwide population-based data sets. The first data set was the Taiwan birth certificate registry published by the Department of Internal Affairs, Taiwan. The Taiwan birth certificate registry includes data on the birthdates of both infants and their parents, gestational week at birth, infant birth weight, gender, parity, place of birth, parental educational level, and maternal marital status.

The second data set was the Taiwan National Health Insurance Research Dataset (NHIRD), published by the Taiwan National Health Research Institute. Taiwan initiated its National Health Insurance (NHI) programme in 1995, with about 99% of the Taiwanese population ( $n=23.72$  million) being enrolled in this programme in 2009. The NHIRD, which is released annually to scientists in Taiwan for research purposes, includes all the original medical claims data and registered files collected under the Taiwan NHI programme. The longitudinal nature of the NHIRD allows researchers to trace the use of medical services by all enrollees since 1995.

The Bureau of the NHI helped link the two data sets using each mother's unique personal identification numbers. All personal identifiers were encrypted before release to researchers. Since the data sets used in this study consisted of de-identified secondary data released to the public for research purposes, it was exempt from full review by an Institutional Review Board.

### Study sample

A total of 473 529 pregnant women who had singleton live births in Taiwan between January 1, 2001, and December 31, 2003, were identified from the NHIRD. If a woman had multiple births during the study period, we only included their first singleton birth in the study sample. Among these singleton deliveries, 163 612 women underwent CS. We excluded those women who had been diagnosed with herpes zoster within 1 yr preceding their index deliveries ( $n=1117$ ). These resulting 162 495 women who underwent CSs were included for analysis. Among the 163 612 CSs, 21 454 women received general anaesthesia and 141 041 received regional (spinal or epidural) anaesthesia.

We individually tracked each sampled woman for 1 yr starting from their index delivery to identify those who had been diagnosed with herpes zoster (ICD-9-CM code 053) during the follow-up period. The independent variable of interest (a diagnosis of herpes zoster) was treated as a dichotomous category based on whether or not a woman received general anaesthesia.

This study also took potential confounders into consideration during regression modelling. These confounders

included maternal characteristics (age, marital status, highest educational level, family monthly income, and emergency CS) and infant characteristics (infant's sex and parity).

### Statistical analysis

The SAS statistical package (SAS System for Windows, Version 8.2, SAS Institute Inc., Cary, NC, USA) was used to perform statistical analyses in this study. We used Pearson's  $\chi^2$  tests to explore differences in maternal and infant characteristics between women who received general anaesthesia and those receiving regional anaesthesia. The log-rank test was used to compare difference in 1 yr cumulative survival times between women who received general or regional anaesthesia.

Cox' proportional hazards regressions stratified by a propensity score were carried out to compute the adjusted 1 yr herpes zoster-free survival rates between these two groups. We calculated a propensity score for each patient. A propensity score was used initially to balance patient and treatment characteristics, which were distributed unequally between general and regional anaesthesia groups. Since the probability of receiving general anaesthesia depends on the opinion of both the physician and the patient, variables for physician's age and sex, and maternal age, marital status, highest educational level, family monthly income, and emergent CS, and also infant's sex and parity, were entered into a multivariable logistic regression model as predictors to calculate the expected probability of receiving general anaesthesia for each patient. Patients were subsequently grouped into deciles based on their propensity score. Subsequently, the model was stratified by a propensity score in deciles to ensure that within each stratum, comparisons were made for patients with a similar expected probability of receiving general anaesthesia and, to a large extent, a similar distribution of confounders. We presented hazard ratios (HRs) along with the 95% confidence intervals (CI). As age is the weightiest risk factor for herpes zoster,<sup>8</sup> the HR adjusted for age alone was reported first, followed by the HR adjusted for all potential confounding factors. A two-tailed value of  $P<0.05$  was deemed statistically significant.

## Results

Women receiving general anaesthesia were more likely to be older (mean age=29.8 vs 29.3 yr,  $P<0.001$ ), unmarried ( $P<0.001$ ), have lower education levels ( $P<0.001$ ), lower monthly incomes ( $P<0.001$ ), and have undergone emergency CS ( $P<0.001$ ) (Table 1). In addition, women receiving general anaesthesia had a greater tendency to have infant parities of three or more than women receiving regional anaesthesia ( $P<0.001$ ).

The incidence of herpes zoster in the year after index delivery was significantly higher in the general anaesthesia cohort (0.46 vs 0.34%,  $P=0.005$ ; Table 2). The absolute risk reduction was 0.12% (95% CI=0.03–0.23), with a number

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