GYNECOLOGY

Immortal time bias in drug safety cohort studies: spontaneous abortion following nonsteroidal antiinflammatory drug exposure

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OBJECTIVE: Experimental research of drug safety in pregnancy is generally not feasible because of ethical issues. Therefore, most of the information about drug safety in general and teratogenicity in particular is obtained through observational studies, which require careful methodologic design to obtain unbiased results. Immortal time bias occurs when some cases do not "survive" sufficient time in the study, and as such, they have reduced chances of being defined as "exposed" simply because the durations of their follow-ups were shorter. For example, studies that examine the risk for spontaneous abortions in women exposed to a drug during pregnancy are susceptible to immortal time bias because the chance of drug exposure increases the longer a pregnancy lasts. Therefore, the drug tested may falsely be found protective against the outcome tested. The objective of the current study was to illustrate the extent of immortal time bias using a cohort study of pregnancies assessing the risk for spontaneous abortions following nonsteroidal antiinflammatory drug exposure.

STUDY DESIGN: We assembled 3 databases containing data on spontaneous abortions, births and drug dispensions to create the present study's cohort. The risk for spontaneous abortion was assessed using 2 statistical analysis methods that were compared for 2 definitions of exposure (dichotomous, exposed vs unexposed, regular Cox regression vs Cox regression with time-varying exposure).

RESULTS: Significant differences were found in the risk for spontaneous abortions between the 2 statistical methods, both for groups and for most specific nonsteroidal antiinflammatory drugs (nonselective Cox inhibitors — hazard ratio, 0.70; 95% confidence interval, 0.61—0.94 vs hazard ratio, 1.10; 95% confidence interval, 0.99—1.22 for dichotomous vs time-varying exposure analyses, respectively). Furthermore, a significant correlation was found between the median misclassified immortal time for each drug and the extent of the bias.

CONCLUSION: Immortal time bias can easily occur in cohort studies assessing the risk for adverse pregnancy outcomes following exposure to drugs. One way to prevent such a bias is by defining exposure only from the time of exposure during follow-up onward using a time-varying exposure analysis.

Key words: ibuprofen, immortal time bias, miscarriage, NSAIDs, spontaneous abortions

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Experimental research of drug safety is generally not feasible because of ethical issues. Therefore, most of the information about drug safety in general and teratogenicity in particular is obtained through observational studies,[1] which require careful methodologic design to obtain unbiased results on which valid conclusions can be based.[2]

One source of bias in retrospective cohort studies of drug safety is created by inappropriate definitions of exposure, leading to "immortal time bias."[3-5] An immortal time bias can result when, during the follow-up period, patients participating in the study develop the outcome under investigation (eg, death or miscarriage) before they have had the chance to be exposed to the medication tested, simply because the duration of the follow-up period was too short, ie, the patient did not "survive" sufficient time to be able to receive the drug. As a result, patients in the study who survive longer have a higher chance of being defined as "exposed."

Figure 1 shows a hypothetical scenario in which this bias can be created. Suppose there were 2 women in the study who conceived on the same day. After exposure to nonsteroidal antiinflammatory drugs (NSAIDs) in her 15th gestational week, the first woman ended the follow-up period without an "event"

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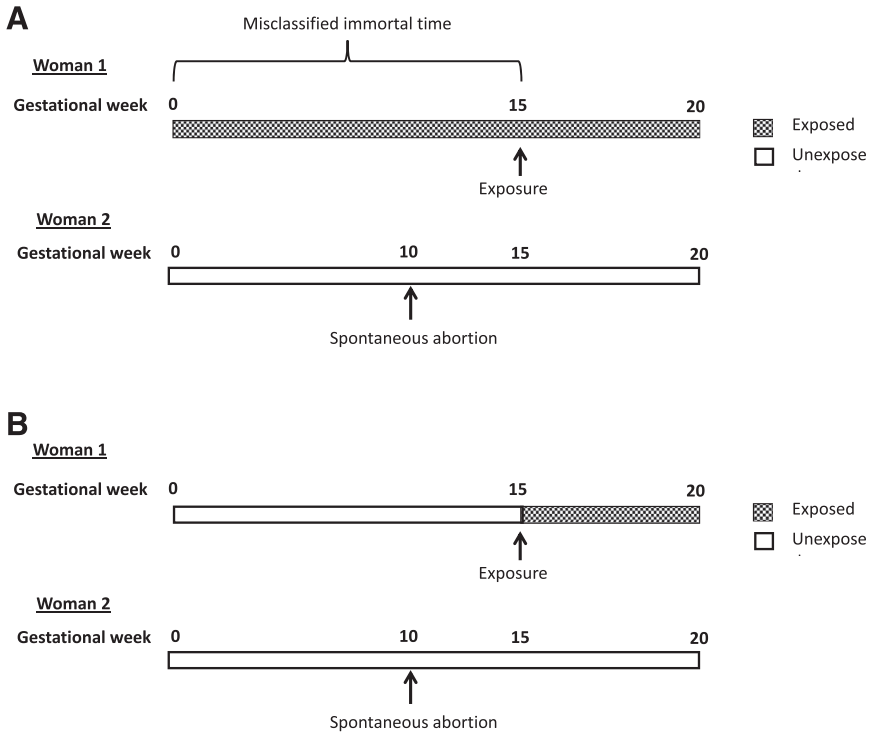
FIGURE 1
Illustration of immortal time bias in cohort studies of drug safety during pregnancy



Definition of exposure **A**, not controlling vs **B**, controlling for immortal time bias.

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(a spontaneous abortion) and gave birth. In contrast, the second woman had a spontaneous abortion on the 10th gestational week, before being exposed to the drug. If a nontime-varying exposure statistical analysis (a logistic regression or Cox regression) was used, the first woman, who gave birth, would be assigned to the "exposed" group whereas the second woman, who had a spontaneous abortion at 10 gestational weeks, would be assigned to the "unexposed" group (Figure 1, A). The period of time during which the first woman was followed (20 weeks) was twice that of which the second woman was followed (10 weeks), and therefore, the first woman, who gave birth, was twice as likely to be assigned to the "exposed" group compared with the second women, who had a spontaneous abortion. Hence an association would be found such that NSAIDs had a protective effect against spontaneous abortions. However, this spurious protective effect was caused not by the drug itself, but rather, by the study's design.

In contrast, with a time-varying exposure analysis, the exposed and unexposed groups are not defined dichotomously (as "exposed" vs "unexposed") from the beginning of the follow-up period. Rather, exposure is redefined during follow-up, such that a woman is counted for as "exposed" only from the period of time that follows the actual exposure. Woman 1, in that case, would only be counted for as exposed from the 15th gestational week onward (Figure 1, B).

Another way of addressing this bias is by presenting the Cox regression model which estimates the hazard for an event (eg, a spontaneous abortion) during follow-up, such that the risk profile (ie, exposure to NSAIDs) is compared at each event time between subjects who developed the event under study (ie, women who experienced a spontaneous abortion) and subjects who stayed in the study at that time point. By defining exposure dichotomously ("exposed" vs "unexposed") among women throughout the whole follow-up period, a misclassification of the risk profile occurs—women who were exposed to NSAIDs only in a point of time during follow-up are misclassified as "exposed" for the period of time before the actual exposure. Because women who gave birth "survive" longer in follow-up and hence have a higher chance of using NSAIDs, this misclassified period of time is more likely to occur in women who did not experience a spontaneous abortion, therefore NSAIDs would be found protective against spontaneous abortions. Hence, a varying exposure analysis enables the redefinition of exposure, such that a woman would be counted for as "unexposed" from the beginning of follow-up to the time of actual exposure.

Three studies have addressed the potential bias in the association between risk factors and adverse pregnancy outcomes by referring to none time-varying exposure during pregnancy as anytime during-pregnancy exposure.[6-9]

The aim of the current study was to illustrate the extent of the bias using a recently published retrospective cohort study that assessed the association between exposure to NSAIDs and spontaneous abortions.[10]

Materials and Methods

Detailed descriptions of the databases and definitions of the variables used in the present study were published recently.[10] We conducted a population-based retrospective cohort study whose participants included all 15- to 45-year-old women who registered with Clalit Health Services health maintenance organization, who conceived between January 2003 and December 2009, and who were admitted for birth or were diagnosed with spontaneous abortion at Soroka Medical Center.

To create the cohort for the current study, we combined 3 computerized databases in which patients are listed according to their personal identification numbers (unique numbers assigned to