Interpregnancy interval and severe maternal morbidity – What can we learn from vital records data?

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Despite the extensive literature on the relationship between interpregnancy interval and foetal-infant outcomes in the subsequent pregnancy,¹² few studies have examined associations between interpregnancy interval and maternal outcomes, particularly in high-resource settings. In low- and middle-income settings, short interpregnancy interval has been associated with increased risks of severe maternal morbidity and maternal death.³ A recent systematic review by Hutcheon and colleagues,⁴ published in the Journal’s January 2019 Special Issue on Birth Spacing in the United States, identified only seven studies from 1966 through 2017 that met inclusion criteria for methodological quality and examined interpregnancy interval and maternal outcomes in high-resource settings, with most focused on less severe maternal outcomes, such as obesity at the conception of the subsequent pregnancy or gestational diabetes.

In this issue of Paediatric and Perinatal Epidemiology, De Silva and Thoma describe their study which used US vital statistics birth certificate data to examine associations between interpregnancy interval and severe maternal morbidity types.⁵ This paper contributes uniquely to this literature by examining maternal morbidity types separately, which enables detection of heterogeneous associations between interpregnancy interval and important maternal morbidity types. De Silva and Thoma found that relationships between interpregnancy interval and severe maternal morbidity varied qualitatively by morbidity type and concluded that this heterogeneity should be considered in birth spacing counselling and recommendations. Despite the novelty and potential importance of these findings, the poor quality of vital statistics data limits the conclusions that can be drawn from this study alone. Associations between interpregnancy interval and specific severe maternal merit further examination in higher quality data sets before these findings are incorporated into pregnancy spacing recommendations or used to inform clinical counselling.

The main limitations of these data for studying interpregnancy interval and severe maternal morbidity are (a) records for successive births to the same mother are not linked, (b) interpregnancy intervals are restricted to those ending in livebirth and (c) severe maternal morbidity is substantially under-reported. The implications of these data quality limitations on the analysis and conclusions of this study are described below.

First, confounding control is limited by the fact that records for successive births to the same mother are not linked. Confounding control is important in studies of interpregnancy interval, given the substantial debate in the literature regarding whether previously reported associations between interpregnancy interval and adverse outcomes are causal or merely reflect confounding by other factors such as maternal age, pregnancy intention, socioeconomic status or outcome of the index pregnancy.⁶ Records for the subsequent pregnancy do not contain detailed information on the outcome of the previous pregnancy. Thus, without linking records for successive births, observed associations may be biased due to unmeasured confounding by outcome of the index pregnancy.

Those confounding variables that are measured in the Vital Statistics files are ascertained at the time of the subsequent birth, which is not the correct time point. The delivery of the index pregnancy serves as the ‘baseline’ (ie the time point at which exposure groups should be balanced in their characteristics), and confounding variables should be measured at or before the start of the interval. The timing for covariate ascertainment is particularly important for variables that change over time for individuals and is critical for variables that may be altered by the interval itself. Adjusting for variables that occur, or are measured, at the conception or delivery of the subsequent pregnancy or thereafter may induce bias. This concern was described in a recent commentary authored by an expert panel on pregnancy spacing convened by the US DHHS Office of Population Affairs.⁷ In the current paper, aside from maternal...
age, information on other confounding variables was measured at the start of the subsequent pregnancy (e.g., pre-pregnancy body mass index (BMI), pre-pregnancy smoking). These variables may be affected by the interpregnancy interval; thus, adjustment may result in an 'over-adjustment' bias due to conditioning on a mediator on the causal pathway from exposure to outcome (structure shown in Figure 1A).\(^8\) This bias may be particularly pronounced due to adjustment for BMI, as women with short intervals are more likely to have higher BMIs at the start of the subsequent pregnancy, perhaps due to less time to lose postpartum weight from the index pregnancy.\(^7\) Thus, adjustment for BMI measured pre-subsequent pregnancy may bias observed associations towards the null (observed risk ratio is closer to the null value of 1 than the true risk ratio).

Secondly, because the measure of interpregnancy interval in vital statistics records is restricted to intervals ending in livebirth, subsequent pregnancies ending in miscarriage, termination or stillbirth are excluded. This distorts the measure of interpregnancy interval for women with an intervening pregnancy loss between livebirths by including both the time between the first livebirth and the loss and time between the loss and the subsequent livebirth. Furthermore, by excluding subsequent stillbirths, risks of severe maternal morbidity may be underestimated. In 2019, Wall-Wieler and colleagues found that severe maternal morbidity risks were 4.8 times higher (95% CI 4.5-5.0) among women with a stillbirth compared with women with a livebirth.\(^9\)

To the extent that interpregnancy interval is associated with stillbirth risk, excluding stillbirths from the analysis would bias estimates of the
association between interpregnancy interval and severe maternal morbidity, following the bias structure depicted in Figure 1A. By excluding stillbirths, the portion of the interpregnancy interval–severe maternal morbidity association that is through the stillbirth path will be ‘adjusted away’, likely underestimating the true association between pregnancy spacing and severe maternal morbidity.

Finally, as De Silva and Thoma note, outcome misclassification in their study was substantial, with sensitivities ranging from 12% to 30%, as reported in a validation study from Massachusetts. Previous validation studies indicate variability in missingness across variables and states (eg 63.3% sensitivity for previous caesarean delivery in New York compared with 91.0% in Vermont and 42.0% sensitivity for gestational diabetes in Florida compared with 70.3% in New York and 75.5% in Vermont). With this degree of state-by-state variability, even reported sensitivity values for severe maternal morbidity types may not apply to the (near) national sample used in this study.

The authors conducted a series of probabilistic bias analyses to examine the potential impact of outcome misclassification on the observed associations under the assumptions of non-differential and differential misclassification with respect to interpregnancy interval. While a laudable approach and worthwhile given severe outcome under-reporting (misclassification), the correction method used relies on the assumption that misclassification is not dependent. That is, the error leading to misclassification of the outcome cannot share common cause(s) with any error leading to misclassification (or missingness) of the exposure. As described by Thoma, De Silva, and MacDorman in 2019, interpregnancy interval is missing more often than most other data items in vital statistics records (5.6%, attributed mostly to missingness for interbirth interval) and is more often missing for older mothers, those of non-Hispanic Black race, and with lower educational attainment. Misclassification of interpregnancy interval was not examined.

If, however, misclassification of interpregnancy interval in these data shares a common cause or common causes with misclassification of severe maternal morbidity (as shown in Figure 1B), these bias analyses would not be valid. One potential common cause of misclassification of both exposure and outcome is state, given the variability in measurement error for clinical variables by state. It may also be that misclassification is more or less likely for some women, either those with more complicated births or with unremarkable births, for example, or for those with more complicated or unremarkable social or economic contexts. Under dependency of misclassification, it is difficult to make general conclusions about reported associations (even after correction), because estimates could be biased, and direction or magnitude of bias are not known.

This paper makes a unique and important contribution to the literature on interpregnancy interval and maternal outcomes and will hopefully prompt future work to examine relationships between interpregnancy interval and severe maternal morbidity types (in particular examining types of maternal morbidity separately). Within the constraints of these data, De Silva and Thoma followed methodological best practices for interpregnancy interval studies: they appropriately defined interpregnancy interval rather than interbirth interval by subtracting the gestational period of the subsequent pregnancy, appropriately adjusted for maternal age measured at the time of the index (pre-interval) birth rather than at the subsequent birth, restricted analyses to intervals following livebirth in the index pregnancy, and used the recommended categories to compare short and long intervals with a referent length of 18–23 months. However, the specific limitations of the vital statistics data for interpregnancy interval and severe maternal morbidity mean that these associations are best interpreted as new hypotheses that merit further exploration in more detailed data sets, rather than as confirmed associations that should be incorporated into clinical recommendations or counselling on birth spacing.

The limitations of the US birth certificate files are unfortunate, as this data source does enable examination of exceedingly rare outcomes, such as subtypes of severe maternal morbidity. Efforts to improve data quality from routine, administrative data sources (such as US vital statistics birth files) would greatly enhance the utility of these data sources for research. In particular, linking records for successive births to the same mother and minimising misclassification of important outcomes (severe maternal morbidity, as well as other birth outcomes of public health importance) would improve researchers’ ability to draw stronger conclusions.

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