The uncertain role of interpregnancy interval and why we need new approaches to an old problem

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Conflict of interest: The authors have no potential conflicts of interests to disclose.

Word count: 590

Interpregnancy interval, if causally linked with adverse perinatal health outcomes, is a potentially modifiable risk factor which can be targeted through public health intervention to improve maternal and child health. However, it currently remains unclear whether interpregnancy interval has a true causal impact on perinatal health. Recent published maternally-matched studies have cast some doubt on this effect, raising the possibility that uncontrolled confounding has driven many of the previous findings supporting these associations. Even amongst matched studies investigating the impact of interpregnancy interval, results have been highly heterogenous,[1] with conflicting evidence for harm from short or long intervals.[2-5] The uncertainty provoked by these recent matched studies necessitates further investigation, and different approaches have much to offer in this regard.

While useful for assessing exposure-outcome relationships, matched designs bear their own challenges. As highlighted by Hutcheon & Harper,[6] matched models may be susceptible to residual within-mother temporal confounding. These studies also have greater set-up requirements, including longer follow-up to observe three or more births (to enable matching of two or more intervals) and linkage of pregnancies to the same woman. Furthermore, results of matched studies may not apply to recurring events, as these are excluded from analysis as concordant strata. Despite these limitations, matched designs provide the opportunity to explore the role of unmeasured time-invariant confounding and how this may influence our understanding of interpregnancy interval. As a result, matched designs are useful methods for establishing evidence in relation to pregnancy spacing recommendations.

In our study, we applied a matched design to the investigation of the perinatal health impacts of a single interval per mother.[7] Unlike a classical matched study on interpregnancy interval, we included an observation for a woman's first birth, as this allows adjustment for risk

factors from the first pregnancy which does not have an interpregnancy interval. Because maternal risk factors are shared across both first and second births and both births are used to adjust for these factors, adjustment is made using within-mother information. This also allowed for the inclusion of women with fewer than three children, representing 63% of multiparous pregnancies in our sample. Our model further adjusted for factors which vary at an individual-level between pregnancies. When adjusting for confounders that vary between pregnancies (i.e., maternal age), which the simulation study did not,[6] the effect of interpregnancy interval is not conditioned out. As is the case with case-crossover designs, only discordant pairs contributed data to the model. While this reduces the analytic sample size and has implications for power and precision, exclusion of concordant pairs is not necessarily a flaw of the design. This exclusion is analogous to case-crossover designs, which have proven to be valuable tools in further evaluating the potential impacts of other perinatal exposures.[8,9]

In the absence of randomized trials, we agree with Hutcheon and Harper[6] that further investigation employing complementary methods are still needed in order to provide appropriate guidance for family planning. Should future studies confirm there is little impact of short or long interpregnancy interval, other factors may take precedence in a family's decision-making, such as desired family size, maternal age, and other family circumstances. Matched designs are not intended to replace unmatched designs. Rather, they offer us the opportunity to re-evaluate the influence of interpregnancy interval from an alternative perspective to previous unmatched cohort studies. Given the uncertainty around the effects of interpregnancy interval and the need to provide evidence-based recommendations to families, we believe further investigation is warranted, and novel approaches using complementary

study designs (which have historically been under-utilized in this area) will be important for providing such evidence.

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