

# Interpregnancy Interval and Pregnancy Outcomes

## *Causal or Not?*



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Interpregnancy interval—the time from the end of one pregnancy to the conception of the subsequent one—can be potentially modified. The critical question is whether such modification improves the outcome of the subsequent pregnancy. There is extensive literature, going back decades, consistently documenting that women who become pregnant again shortly after delivery of a viable neonate are at increased risk of giving birth to a preterm, low birth weight, or small-for-gestational age neonate in the subsequent pregnancy.<sup>1</sup> Indeed, the World Health Organization recommends an interval of at least 24 months after a live birth for a woman to become pregnant again.<sup>2</sup> The literature on pregnancy outcomes after long intervals is more recent, somewhat less consistent, and more susceptible to confounding by unreported miscarriages or voluntary terminations, secondary infertility, and partner changes, but suggests similar findings. Consistency of results is a criterion for causality,<sup>3</sup> but in applying it we must consider whether consistency might be due to multiple studies sharing a common flaw.

The first clue that a common flaw might account for the apparent increased risk of short intervals was published by Erickson and Bjerkedal almost 40 years ago.<sup>4</sup> They took advantage of extensive record linkage in Norway to evaluate prospectively the effects of interpregnancy interval when information was available on the birth weights of both the child whose birth started the interval and the child whose conception ended it.<sup>4</sup> They confirmed the expected association of short intervals with low birth weight in the second child, but they also reported that the birth weight of the first child had an identical association with interval as did the birth weight of the second. They concluded that women who were already at high risk for a low birth weight neonate tend to become pregnant again right away, but that short interpregnancy interval per se might not be causal for low birth weight. Virtually every other report that evaluated the association of interpregnancy interval and pregnancy outcome used cross-sectional data rather than the longitudinal data employed by Erickson and, as such, had very little information on the woman's inherent risk of an adverse pregnancy outcome, independent of interval.

In 2014, a group from Australia used a longitudinally linked database similar to the one in Norway, but they went beyond the work of Erickson by employing a design not previously used to study interpregnancy interval.<sup>5</sup> They studied women who had three singleton pregnancies and therefore had two interpregnancy intervals (from the birth of the first to the conception of the second and from the birth of the second to the conception of the third child). This enabled each woman to serve as her own control in a case-crossover study.<sup>6</sup> In effect, they are answering the question, “Is the risk of an adverse outcome in a pregnancy after a very

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short or very long interpregnancy interval greater than the risk of an adverse outcome in a pregnancy experienced by that very same woman after a more typical interval?"

The case-crossover design has several advantages. By comparing a woman with herself, it inherently controls perfectly for characteristics that do not change, such as genetics or early life exposures. It provides nearly perfect control for characteristics that are unlikely to change substantially between pregnancies, such as socioeconomic status or education. It accomplishes this control without the need to actually measure these characteristics. The results can easily be refined further by simple statistical control for factors that change between pregnancies, such as parity or smoking.

The case-crossover design also has some limitations. It cannot control for unmeasured factors that change between pregnancies. Indeed, if there are many important, unmeasured factors that change, it can produce results that are more biased than a conventional design.<sup>7</sup> Because a woman is being compared with herself, only those women who had an adverse outcome in one but not the other of their second and third pregnancies and whose two interpregnancy intervals were different from each other can be included. Women who had only normal outcomes or only abnormal outcomes in both their second and third pregnancies do not have a comparison pregnancy, and women with identical intervals have the same exposure in both pregnancies; thus, both are excluded by design. This means that large databases are needed. For example, the Australian group report that only 5–10% of women with three pregnancies could be included in the analysis.<sup>5</sup> Even when large databases exist, study power might be limited.

In this issue of *Obstetrics & Gynecology*, Hanley et al (see page 408) report on a case-crossover analysis of longitudinally linked records for all births of at least 20 weeks of gestation in British Columbia.<sup>8</sup> They found no evidence of increased risk of preterm birth, small for gestational age, low birth weight, or neonatal intensive care unit admission among neonates born after a short interpregnancy interval, and minimal evidence of increased risk of these outcomes after very long intervals, as compared with siblings born after more typical intervals. When they analyzed the same data using a conventional analysis, they were able to replicate the conventional results of increased risk after short and long intervals, which gives us confidence that the case-crossover results are not the result of having studied an atypical population. A novel finding of this study is that short interpregnancy

intervals were associated with increased risk of both gestational diabetes and being obese at the beginning of the subsequent pregnancy in both the conventional and case-crossover analysis. Although these results need to be confirmed in additional studies, they appear intuitively plausible.

Since Hanley et al drafted their article, two additional case-crossover studies of interval have been published. One, from the Netherlands, studied subsequent intervals in women whose first birth was preterm<sup>9</sup> and as such might not apply to the general obstetric population. The authors noted increased risk of preterm birth with very short intervals in these women.<sup>9</sup> The other, based on more than 300,000 women in California,<sup>10</sup> found that, although the elevated risk in the case-crossover analysis was less than in the conventional analysis, short (less than 6 months) intervals still had a modest, but statistically significant, 20% relative increase in risk of preterm birth compared with intervals of 18–23 months. Long intervals were not associated with increases in preterm birth. When I combined all the studies in a meta-analytic model, the results demonstrated substantial statistical heterogeneity (I-squared=80%; 85% excluding the Dutch study) for short intervals, precluding a blanket statement.

So where do these studies leave us? I believe they allow me to reinforce and extend my previous summary and recommendations<sup>11</sup>:

- All parturient women should leave the hospital fully aware of how quickly they might become pregnant again and with firm plans for effective and appropriate contraception should they not wish to become pregnant at that time.
- It is virtually certain that any harmful effect of very short or very long intervals is less than older studies have indicated.
- The three general-population studies that compared a woman with herself disagree on whether there is any harm at all of short intervals regarding adverse neonatal outcomes in the subsequent pregnancy, although they are generally supportive of long intervals not having an increased risk of most adverse neonatal outcomes.
- Women whose pregnancies were uncomplicated and who are in good health can be advised that decisions regarding timing of subsequent pregnancies should be based primarily on personal desires regarding child spacing and ultimate family size and only secondarily on obstetric concerns.
- Additional research is needed to confirm whether short interpregnancy interval affects subsequent pregnancy outcome in women whose initial



pregnancy ended before term, as suggested by the Dutch study.<sup>9</sup> Whether the effect of short intervals varies with delivery route of the first birth is also worthy of investigation. This additional work could easily be accomplished within the Australian, Californian, and Canadian cohorts.

- We should not assume that these results and recommendations apply to populations of women in whom gross clinical malnutrition and untreated chronic infections are common.
- The results regarding gestational diabetes and pre-pregnancy body mass index require replication, but they support recommendations that all women enter pregnancy with the healthiest body mass index possible<sup>12</sup> and that they follow the current recommendations for gestational weight gain from the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine (formerly the Institute of Medicine) and the American College of Obstetricians and Gynecologists.<sup>12,13</sup>

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