**Interpregnancy interval and risk of perinatal death: a systematic review and meta-analysis**

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**Abbreviations:**

CI, Confidence interval

DAG, Directed-acyclic-graph

HIC, High-income country

IPI, Interpregnancy interval

LMIC, Low and middle-income country

NOS, Newcastle-Ottawa Scale

OR, Odds ratio

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis

SDG, Sustainable Development Goal

WBC, World Bank Category

WHO, World Health Organization

**Abstract**

**Background:** Interpregnancy interval (IPI) <6 months is a potentially modifiable risk factor for adverse perinatal health outcomes.

**Objective:** This systematic review evaluated the international literature on the risk of perinatal death associated with IPI.

**Search Strategy:** Two independent reviewers screened titles and abstracts identified in MEDLINE, EMBASE, and Scopus from inception to 4 April 2019 (Prospero Registration# CRD42018092792*)*.

**Selection Criteria:** Studies were included if they provided a description of IPI measurement and perinatal death, including stillbirth and neonatal death.

**Data Collection and Analysis:** A narrative review was performed for all included studies. Random-effects meta-analysis was used to compare unadjusted odds of perinatal death associated with IPI <6 months and IPI ≥6 months. Analyses were performed by outcome of the preceding pregnancy and study location.

**Main Results:** Of the 624 unique articles identified, 26 met inclusion criteria. The pooled unadjusted odds ratio of perinatal death for IPI <6 months was 1.34 (95% CI 1.17, 1.53) following a previous live birth, 0.85 (95% CI 0.73, 0.99) following a previous miscarriage, and 1.07 (95% CI 0.84, 1.36) following a previous stillbirth compared to IPI ≥6 months. However, few high-income country (HIC) studies reported an association after adjustment. Fewer studies evaluated the impact of long IPI on perinatal death and what evidence was available showed mixed results.

**Conclusions:** Results suggest a possible association between short IPI and risk of perinatal death following a live birth, particularly in LMICs.

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**Keywords:** Birth intervals; Birth spacing; Interpregnancy interval; Perinatal death; Stillbirth; Systematic review

**Tweetable Abstract**

Short IPI <6 months after a live birth was associated with greater risk of perinatal death than IPI ≥6 months.

**Introduction**

Annually, 2.7 million pregnancies end in stillbirth and 2.8 million newborns die in the first month of life.1 Global progress in the prevention of stillbirth and early neonatal death has been disappointingly slow.2 Identification and implementation of effective policies and interventions for reducing the risk of perinatal mortality is a global priority for improving newborn health.1, 2

Interpregnancy interval (IPI), or the time between the end of one pregnancy and the conception of a subsequent pregnancy, has been linked to the risk of adverse pregnancy outcomes.3 Specifically, short and long IPIs have been associated with increased risk of pregnancy complications, preterm birth, small-for-gestational-age birth,4-10 and perinatal death.4, 11-15 To reduce the risk of these events, the World Health Organization (WHO) recommends individuals wait at least two years following a live birth and six months following a spontaneous or induced abortion before conceiving again.16 However, the WHO guidelines are now more than 13 years old, and more recently issued guidance by healthcare organisations have suggested an interval 18-24 months following a previous live birth may be optimal.16-18

Previously published reviews have evaluated the impact of short IPI on neurodevelopmental disabilities,19 nutritional status,20 and the effect of IPI after a previous miscarriage on birth outcomes.21 A recent systematic review of research from high-income countries (HICs) identified three studies evaluating the association between short IPI and perinatal death.22 Although short and long IPI effects are also relevant in low- and middle-income (LMIC) country settings and plausibly explain a fraction of perinatal deaths, no international review has been conducted on the association between IPI and risk of perinatal death. This study aims to systematically review the current global evidence on the association between IPI and perinatal death.

**Methods**

***Search strategy and selection criteria***

We conducted a systematic review and meta-analysis in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; Table S1).23 We searched peer-reviewed literature for articles investigating IPI and perinatal death using the PubMed/Medline, EMBASE, and Scopus databases from inception to 4 April 2019. Our search included one string to identify our exposure of interest (interpregnancy interval) in combination with a second string to identify our outcome of interest (perinatal death) (Table S2). The study protocol was registered with PROSPERO (CRD42018092792; 12 April 2018).

Studies were eligible for inclusion if they measured perinatal death by categories of IPI . IPI was defined as the time from the end of one pregnancy (based on date of previous birth) to the start of the next pregnancy (based on either last menstrual period or estimated date of conception). Perinatal death included: i) stillbirth (death from gestational age ≥20 weeks to birth), ii) neonatal death (death from birth to 28 days post-birth), and iii) perinatal death (death from gestational age ≥20 weeks to 28 days post-birth). Deaths from all causes were included. Pregnancies ending in induced abortion or miscarriage before 20 weeks of gestation were not included.

Studies were excluded if they: i) were a review or commentary; ii) were published in languages other than English; iii) did not measure IPI and pre-specified outcomes of interest; or iv) measured only birth-to-birth (interbirth) interval, because it is influenced by the final gestational length of the following pregnancy. Two reviewers (AR, AA) independently screened and reviewed titles and abstracts and performed full-text review of identified articles. A third independent reviewer (GP) resolved any conflicts in the review decisions.

***Data analysis***

For each included study, at least two reviewers independently extracted details of articles (AR, AA, IP, RK), including: author and year published, geographic setting and World Bank Classification (WBC) of countries,24 years of births included in study, study design, sample size, definition of IPI and study outcomes, exposure and outcome frequencies, effect estimates, and adjustment variables included in the model. Because the outcome of the preceding pregnancy has been shown to modify the effect of IPI on birth outcomes,25 when it was provided, outcome of the pregnancy preceding the IPI was also extracted.

Risk of bias was independently assessed for included studies by at least two reviewers (AR, IP, RK) using the Newcastle-Ottawa Quality Assessment Scale (NOS).26 Using this scale, studies were assessed in terms of risk of bias across three domains: sample selection, comparability, and exposure/outcome measurement. The total score possible ranges from zero stars (highest risk of bias) to nine stars (lowest risk of bias): four stars for sample selection, two stars for comparability, and three stars for exposure/outcome measurement.

We performed a narrative synthesis of all included studies, using author-defined categories of IPI. For studies where IPI was categorized in such a way that comparisons were possible (<6 months vs. ≥6 months), we additionally performed meta-analyses. Based on frequency data published in the included studies, we estimated study-level effects of IPI <6 months. Raw frequency data were used to estimate the odds of perinatal death for births following an IPI <6 months as compared to IPI ≥6 months for each study. Where necessary, raw frequencies were combined to create the categories <6 months and ≥6 months. We also calculated and reported the absolute risk difference where possible. We then estimated pooled crude effects comparing the odds ratio (OR) of short IPI (<6 months) compared to IPI ≥6 months using a random-effects meta-analysis with the inverse variance method27 which weights estimates by the standard error of the log odds ratio from each study.27 We applied a random effects meta-analysis as this allowed each study to estimate a different effect size, and given the wide range in the sample size of included studies, allowed for a more balanced approach to weighting in the estimation of a pooled effect. We performed pre-specified subgroup analyses by income category of the country of birth. Further subgroup analyses were performed, specified post hoc, by outcome of the pregnancy preceding the IPI. To quantify statistical heterogeneity of study results, we report the I2 statistic, estimated as I2=100% · (Q-df)/Q, where Q is Cochrane’s heterogeneity statistic and df is the degrees of freedom. I2 indicates the percentage of total variation across studies due to true variation rather than chance and offers a better powered estimate of heterogeneity in cases where few studies are included.28-30 Interpretation of the I2 statistic was made consistent with international guidelines.31 Analyses were performed in STATA/IC version 14.2 (College Station, TX).

***Consumer and Patient involvement***

This study did not involve consumer and community participation (Table S3); however, the results of the study were shared with a community reference research group at Curtin University (Perth, Western Australia).

***Role of the funding source***

This study was funded in part by the National Health and Medical Research Council (Australia; GNT1099655). The funder had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

In total, 624 studies were screened and 110 were deemed potentially eligible (Figure 1); 84 articles were excluded following full-text review leaving 26 articles included in the narrative synthesis. The most common reasons for exclusion were the absence of any comparison of outcomes by IPI (n=27), measurement of interbirth interval rather than IPI (n=23), no investigation of perinatal death (n=19), no inclusion of primary data analysis (n=9), or inclusion of unsuitable outcome variable (n=6).

Seven studies were from Europe (UK: 4; Denmark: 1; Germany: 1; Sweden: 1), five were from US or Canada (US: 4; Canada; 1), five were from Latin America and Caribbean (Brazil: 1; Ecuador: 1; multiple countries: 3), four were from South Asia (Bangladesh: 3; India: 1), two were from sub-Saharan Africa (Cameroon: 1; Tanzania: 1), one was from the Middle East (Kuwait: 1), one was from North Africa (Egypt: 1), and one included multiple HICs (Australia, Finland, and Norway) (Table S4). One included study was a case-control study and the remaining 25 were cohort studies.

Exposure definitions and the reference interval used for estimation of effects varied by study. Definitions of “short” interpregnancy interval was most commonly <6 months (n=17), but ranged from <3 months (n=3) to <24 months (n=3). The longest interpregnancy interval evaluated ranged from ≥24 months (n=8) to ≥120 months (n=1); studies commonly defined “long” IPI as ≥60 months (n=4). Furthermore, different definitions of perinatal death were applied. Most commonly stillbirth was defined as fetal death at a gestational length ≥28 weeks, particularly in studies from LMICs (n=8; LMIC: 6 and HIC: 2). Five studies used a gestational length ≥20 weeks (LMIC: 3; HIC: 2). The remainder used a gestational length between 20 and 28 weeks (n=6; LMIC: 3; HIC: 3) or did not provide a gestational age range for their definition of stillbirth (n=7; LMIC: 1; HIC: 6).

Review of risk of bias indicated that studies generally performed well on the NOS for sample selection and comparability, but performed poorly for exposure/outcome measurement (Table S5). While most studies scored ≥3 stars for sample selection (n=24/26) and 13 studies scored the maximum two stars for comparability, 21 studies scored one star for exposure/outcome measurement. Most studies adjusted for the pregnant individuals’ age (n= 17), education (n=12) or marital or cohabitation status (n=11) (Table S6). Other common covariates included the pregnant person’s smoking (n=8), obstetric history (n=10), parity or birth order (n=8), health conditions (n=7), prenatal care (n=6), body mass index (n=6), or year of the child’s birth (n=6). Studies uncommonly (n<5) attempted to account for other social factors (e.g., socioeconomic status, household size, residence, religion, race/ethnicity), pregnancy intention, and alcohol use.

Among the 16 studies that provided effect estimates for IPI <6 months following any prior pregnancy outcome, six reported a modest increase in risk of perinatal death compared to longer IPIs,25, 32-36 half of which were from LMICs25, 32, 33 (Table S7). Adjusted odds ratios of perinatal death associated with IPI <6 months ranged from 1.54 (95% CI 1.28-1.83)33 to 2.09 (95% CI 1.75, 2.46)32 in LMICs, translating to a 3.1% to 3.4% absolute increase in the risk of perinatal death. With the exception of one HMIC study investigating stillbirth at peri-viable gestation (aOR: 1.55; 95% CI 1.28-1.87),34 no adjusted estimates from a HIC suggested a statistically significant association between IPI <6 months and risk of perinatal death (Range: aOR: 0.90; 95% CI 0.51, 1.59 to aOR: 1.13; 95% CI 0.87, 1.47).11, 36

Of the six studies that examined IPI following a previous miscarriage (LMIC: 3 and HIC: 3),25, 37-41 one study from Egypt identified a significant increase in the adjusted odds of perinatal death for IPI <6 months compared to IPI >12 months (aOR: 2.49; 95% CI: 1.00, 3.90)38 (Table S7). The remainder did not identify a significant association between IPI after a miscarriage and odds of perinatal death (Range aOR: 0.70 [95% CI: 0.38, 1.29] to aOR: 1.31 [95% CI: 0.94, 1.82]). Three studies reported on IPI after a previous stillbirth,25, 39, 42 two of which provided adjusted estimates.25, 42 Davanzo *et al* (2007) reported an adjusted odds ratio of 2.35 (95% CI 1.57, 3.50) for IPI <6 months following a previous stillbirth as compared to IPI 27-50 months following a previous live birth.25 Regan *et al* (2019) reported no significant association between IPI <6 months compared to IPI ≥24 months following a previous stillbirth (aOR: 1.09; 95% CI: 0.62, 1.91).42

Of the 11 studies that provided adjusted estimates measuring the association between longer IPIs and risk of perinatal death, six reported a harmful association.11, 15, 33, 34, 43, 44 Of the three studies reporting on IPI ≥ 60 months after any prior pregnancy outcome in LMICs, one identified an increase in the odds of perinatal death compared to an IPI of 18-23 months (aOR: 1.21; 95% CI 1.15, 1.27).33 The other two studies from LMICs did not identify this association (aOR: 0.75; 95% CI: 0.22, 2.57 and aOR: 1.07; 95% CI: 0.87, 1.32).13, 45 Two HIC studies reported on longer IPIs after any previous pregnancy outcome. Carmichael *et al* (2019) reported an adjusted odds ratio of 1.28 (95% CI 1.14, 1.44) associated with IPI ≥48 months as compared to 6-23 months.34 Stephansson *et al* (2003) reported an adjusted OR of 1.2 (95% CI 1.0, 1.4) after a 36-71 months IPI and 1.5 (95% CI 1.1, 2.1) after a ≥72 month IPI.44 Following a previous live birth, Smith *et al* (2003) found no association between perinatal death and IPI 24-50 months as compared to 18-23 months (aOR: 1.2; 95% CI: 0.7, 2.1).46 Love *et al* (2010) reported an adjusted OR of 1.07 (95% CI: 0.54, 2.15) for IPI >24 months following a previous miscarriage as compared to 6-11 months.40

Of the 26 included studies, 11 were suitable for meta-analysis. The most common reasons for exclusion from meta-analysis was that the IPI categories provided were not comparable (n=8) or that the frequency of outcomes could not be computed from published information (n=4) (Figure 1). In pooled unadjusted analyses, the OR of perinatal death for IPI <6 months compared to ≥6 months following any previous pregnancy outcome was 1.19 (95% CI: 0.84-1.67; absolute risk difference: 3.10%; 95% CI: 2.88, 3.32%), although there was substantial heterogeneity across studies (I2=96%) even when considering LMICs and HICs separately (98% and 36%, respectively) (Figure S1). When we considered pregnancy outcomes separately, we observed a 34% (pooled OR 1.34, 95% CI 1.17-1.53; absolute risk difference: 0.21%; 95% CI: 0.14, 0.28%) increase in the risk of perinatal death associated with IPI <6 months compared to IPI ≥6 months following a previous live birth (Figure 2), with little statistical heterogeneity (I2 <0.1%). The unadjusted association between IPI <6 months after a live birth and perinatal death was similar in studies conducted in LMIC versus HIC countries (LMIC pooled OR: 1.43, 95% CI 1.08-1.87; HIC pooled OR: 1.33, 95% CI 1.17-1.51) (Figure 3).

For IPI <6 months following a miscarriage, the pooled odds ratio suggested there was a significant reduction in the odds of perinatal death compared to longer IPI (pooled OR: 0.85; 95% CI 0.73, 0.99; absolute risk difference: 0.10; 95% CI: -0.15, 0.35%) with little variation in study findings due to heterogeneity (I2<0.1%). When we evaluated the association between IPI <6 months after a miscarriage and risk of perinatal death, we identified similar results for LMICs (pooled OR: 0.87, 95% CI 0.70-1.07) and HICs (pooled OR: 0.80, 95% CI 0.62-1.05), although these pooled estimates were not statistically significant (Figure 4).

For IPI <6 months following a stillbirth, IPI <6 months was not associated with an increase in the odds of perinatal death (pooled OR: 1.07; 95% CI: 0.84, 1.36; absolute risk difference: 0.03; 95% CI: -0.47, 0.53%), although there was substantial heterogeneity in study results (I2=74.7%)(Figure 2).

**Discussion**

***Main findings***

Although the unadjusted association between IPI <6 months and odds of future perinatal death was similar in LMIC and HIC settings, after confounding variables were taken into account, this association was not evident in HICs. This association was also not evident for births following a previous miscarriage or stillbirth and was difficult to assess for long IPI. Although several LMIC studies indicated IPI >24 months and two HIC studies indicated IPI ≥36 months was associated with increased occurrence of perinatal death, the remaining studies suggesting no association or evaluating longer intervals. However, given the considerable variation in the definition of IPI categories across the included studies, additional future research applying consistent IPI and outcome definitions would be useful for further evaluating the perinatal health impacts of IPI.

***Strengths and Limitations***

This review included a large body of evidence spanning 33 countries over almost four decades. Where possible, we were able to combine evidence across multiple studies within LMICs and HICs, generating a comprehensive assessment of the existing literature. Furthermore, this study conformed to recommended guidelines for conducting systematic reviews (i.e., PRISMA) and meta-analyses (i.e., MOOSE). Despite these strengths, this review had several limitations. First, we restricted the review to studies published in English, which may have biased the representation of included studies. However, we identified relatively few articles published in a language other than English; we were able to include studies from 33 countries, suggesting this criterion did not substantially impact the geographic representation of the evidence included in this review. Second, we used the NOS to quantify risk of bias in the individual studies, and although the NOS is a widely utilized and previously validated tool,26 it has its limitations, including potential over-emphasis on the generalizability of the exposed cohort and arbitrary selection of important confounders.47

Additional methodological considerations limited the quality of some studies included in our meta-analyses and reduced our ability to perform more comprehensive meta-analyses. First, there was substantial clinical and methodological heterogeneity in the studies identified in terms of exposure and outcome definitions and study quality. LMICs more commonly used broad IPI categories, which made inclusion of higher quality LMIC studies in meta-analyses impractical. The broad categorization of long IPIs in both LMIC and HIC studies also prohibited meta-analysis of longer IPI categories. Ultrasound dating and use of vital records were more frequently available in HICs, while last menstrual period (LMP) and personal interview or hospital records were used more frequently in LMICs. Stillbirth was most commonly defined as fetal death at ≥28 weeks for LMICs, whereas studies in HICs used ≥20 weeks or provided no definition by gestational age. Furthermore, several studies adjusted for variables which may lie on the causal pathway, including the gestational age and birthweight of the index pregnancy.11, 33, 43 As a result, it is possible that overadjustment bias may be present in some of the studies. The use of directed-acyclic-graphs (DAGs) would be helpful in ensuring inclusion of an appropriate minimum set of confounding variables.48

***Interpretation***

Results from this review suggest short and long IPI may be associated with increased risk of perinatal death; however, these associations varied by geographic setting and prior obstetric outcome. Several explanations for the variability in study findings are possible. Results from studies which did take into account the outcome of the preceding pregnancy had the widest variation. Furthermore, we observed reduced heterogeneity across study results in subgroup analyses that factored for outcome of preceding pregnancy. This implies the outcome of the preceding pregnancy is an important consideration when estimating IPI effects. Unadjusted analyses suggested a 34% increase in the odds of perinatal death associated with IPI <6 months after a live birth. In contrast, there was no indication that IPI after a miscarriage was associated with increased risk of perinatal death in the subsequent pregnancy.25, 40 These findings are consistent with a previous systematic review of the effects of IPI after miscarriage, which found that conception within six months of a miscarriage was associated with the lowest odds of miscarriage in the next pregnancy,21 suggesting short IPI following a previous miscarriage may not be harmful to the subsequent pregnancy. This conclusion is inconsistent with the current WHO birth spacing guidelines, which recommend waiting at least six months after a miscarriage before becoming pregnant again.16 However, the WHO birth spacing guideline is based on evidence available in 2005 and because more recent evidence conflicts with some of its recommendations, there have been calls to revisit global birth spacing recommendations accordingly.49 We agree that the recommendations need to be reviewed.

Our review of the IPI literature indicates several areas where additional research would be valuable. Most notably, we observed substantial clinical and methodological heterogeneity in existing studies, which makes comprehensive assessment of the health impacts of birth spacing difficult; international studies applying standardized methodology across LMICs and HICs would allow for a more comprehensive assessment of IPI, especially for longer intervals. Based on our review, for future IPI studies, we would recommend 1) consistent categorization of IPI; 2) performing analyses by prior obstetric outcome; and 3) collection of a comprehensive list of sociodemographic and clinical variables. Future research which applies the same categories would facilitate comparison to previous studies. As the most frequent categorization of intervals following a live birth was 0-6 months, 6-11 months, 12-17 months, 18-23 months, 24-59 months, 60-119 months, and ≥120 months, using 18-23 months as the reference category, these may be useful categories to report - as a minimum - in future research.

We identified few studies that evaluated the effects of IPI after a stillbirth. Fifteen years after the WHO birth spacing guideline was published, we found only three studies evaluating effects of IPI after a previous stillbirth,25, 39, 42 and just one which reported adjusted estimates for odds of stillbirth after a previous stillbirth by categories of IPI.42 Among the three published studies, unadjusted results were inconsistent. The one study reporting adjusted estimates suggested no adverse association with IPI.42 This limited evidence poses challenges to making evidence-based guidelines for optimal IPI after a stillbirth, and further research focusing on IPI after stillbirth would be useful.

**Conclusion**

Recommendations for optimal birth spacing are important for planning future pregnancies. Although several LMIC studies suggested a possible association between short and long IPI and risk of perinatal death following a previous live birth, evidence from HICs indicated no elevated risk of perinatal death associated with short IPI. There was limited evidence suggesting an association between IPI after miscarriage or stillbirth in LMICs and HICs. Given the variation in study protocols and limited evidence on IPI after a previous stillbirth, further high-quality evidence across LMICs and HICs is needed to appropriately guide global recommendations for optimal IPI.

**Contribution to Authorship**

AR designed the study, developed and registered the study protocol, performed all analyses, and oversaw the management of all aspects of the study. All co-authors provided input into the study protocol. AA performed the search and participated in screening, review and extraction. RK and IP led the full-text review and data extraction. LM, CM, AG, and GP advised on analysis and contributed to the interpretation of findings. All co-authors contributed to the writing of the final manuscript and approved the final version for submission.

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**Details of Ethics Approval**

No ethics approval was required for this systematic review; however, the review was prospectively registered with the National Institute for Health Research Prospero International Prospective Register of Systematic Reviews (#CRD42018092792).

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**Figure Titles**

**Figure 1.** Systematic review of the literature evaluating the association between interpregnancy interval and risk of perinatal death.

**Figure 2.** Meta-analysis of unadjusted odds ratios of perinatal death for interpregnancy interval of less than six months compared to interpregnancy interval greater than six months, by outcome of the previous pregnancy.

**Figure 3.** Meta-analysis of unadjusted odds ratios of perinatal death for interpregnancy interval of less than six months following a live birth compared to interpregnancy interval great then six months following a live birth, by World Bank Category.

**Figure 4.** Meta-analysis of unadjusted odds ratios of perinatal death for interpregnancy interval of less than six months following a miscarriage compared to interpregnancy interval greater than six months following a miscarriage, by outcome of the previous pregnancy, by World Bank Category.

**Figure S1.** Meta-analysis of unadjusted odds ratios (OR) of perinatal death for interpregnancy interval of less than six months compared to interpregnancy interval greater than six months, by World Bank Category.

**Figure Legends**

**Figure 2 Legend**.

Abbreviations: OR, odds ratio; CI: confidence interval; DNP, data not provided

\*Weights are derived from random effects meta-analysis

**Figure 3 Legend.**

Abbreviations: OR, odds ratio; CI, confidence interval; DNP, data not provided

\*Weights are derived from random effects meta-analysis.

**Figure 4 Legend**.

Abbreviations: OR, odds ratio; CI, confidence interval

\*Weights are derived from random effects meta-analysis

**Figure S1 Legend**.

WBC, World Bank Category

†Weights are derived from random effects

\*Studies deemed to be moderate to high quality