

# BMJ Open Effects of interpregnancy interval on pregnancy complications: protocol for systematic review and meta-analysis

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## ABSTRACT

**Introduction** Interpregnancy interval (IPI) is the length of time between a birth and conception of the next pregnancy. Evidence suggests that both short and long IPIs are at increased risk of adverse pregnancy and perinatal outcomes. Relatively less attention has been directed towards investigating the effect of IPI on pregnancy complications, and the studies that have been conducted have shown mixed results. This systematic review will aim to provide an update to the most recent available evidence on the effect of IPI on pregnancy complications.

**Method and analysis** We will search electronic databases such as Ovid/MEDLINE, EMBASE, CINAHL, Scopus, Web of Science and PubMed to identify peer-reviewed articles on the effects of IPI on pregnancy complications. We will include articles published from start of indexing until 12 February 2018 without any restriction to geographic setting. We will limit the search to literature published in English language and human subjects. Two independent reviewers will screen titles and abstracts and select full-text articles that meet the eligibility criteria. The Newcastle-Ottawa tool will be used to assess quality of observational studies. Where data permit, meta-analyses will be performed for individual pregnancy complications. A subgroup analyses by country categories (high-income vs low and middle-income countries) based on World Bank income group will be performed. Where meta-analysis is not possible, we will provide a description of data without further attempt to quantitatively pool results.

**Ethics and dissemination** Formal ethical approval is not required as primary data will not be collected. The results will be published in peer-reviewed journals and presented at national and international conferences.

**PROSPERO registration number** CRD42018088578.

## INTRODUCTION

The length of time between birth and the beginning of the following pregnancy (interpregnancy interval (IPI)) has been linked to an increased risk of adverse outcomes in infants and their mothers.<sup>1–4</sup> To reduce this risk, the WHO *and* the American College of Obstetrics and Gynaecology suggest an interval of at least 2 years and a minimum of 18 months following a live birth, respectively.<sup>2,3</sup> IPI is viewed as a potential modifiable

## Strengths and limitations of this study

- The proposed systematic review and meta-analysis will adhere to the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines.
- The review aims to provide an update to the most recent available evidence on the effect of interpregnancy interval on pregnancy complications.
- Two independent reviewers will screen titles and abstracts, study eligibility and perform the quality assessment.
- This review will only include the published literature in the English language.

risk factor for adverse maternal and perinatal outcomes for planned pregnancies.

The importance of birth spacing has been a focus for perinatal researchers and policy-makers for nearly a century.<sup>5</sup> Studies have revealed that both short and long IPIs are potentially associated with increased risk of adverse perinatal outcomes, including stillbirth, small for gestational age, preterm delivery and neonatal death.<sup>1,3,4,6</sup> Conversely, the effect of IPI on complications during pregnancy has received less attention.

There is a growing body of literature that recognises the association between short IPIs and risk of premature rupture of membrane (PROM),<sup>7,8</sup> placental abruption, placenta praevia,<sup>9</sup> uterine rupture for women who previously delivered by caesarean section<sup>10,11</sup> and gestational diabetes.<sup>12</sup> Similarly, long IPIs have long been associated with increased risk of pre-eclampsia<sup>13,14</sup> and labour dystocia.<sup>4</sup>

Although previous reviews<sup>1,15</sup> have suggested that IPI is associated with risk of pregnancy complications, these reviews did not identify a sufficient number of studies to evaluate the effect of IPI on pregnancy complications.

The two systematic reviews investigating the effect of IPI on maternal health/outcomes were published 10 years and 5 years ago,

respectively,<sup>1 15</sup> and there has since been increasing attention paid to this area and a number of publications.<sup>12 16–19</sup> Meanwhile, the reviews have been either limited to few maternal outcomes of interest (ie, maternal haemorrhage, PROM)<sup>9</sup> or not included results from studies published in the last decade.<sup>1</sup> A further systematic review of the effect of IPI on pregnancy complications is warranted, with a view to meta-analysis of the outcomes.

This systematic review will explore the effect of IPI on pregnancy complications. The information obtained from this review is important to inform women, their family and clinicians regarding IPI. The main purpose of the systematic review is to update, compile and critically review the evidence on the effects of IPI on pregnancy complications.

## METHODS AND DESIGN

### Population

The systematic review will include multiparous women with information on length of interval between two consecutive pregnancies. We will not exclude studies that implemented restrictions on age, ethnic group, parity and socioeconomic status.

### Study design

This systematic review will include all observational prospective or retrospective studies that have assessed the effects of IPI with various pregnancy complications according to birth interval categories. Randomised controlled trials (RCT) are unlikely to be identified due to exposure of interest but will be included if available.

### Comparator(s)/control

When assessed as a categorical variable, the reference IPI category will be 18–23 months.

### Outcomes

The outcomes of interest in this review are pregnancy complications, defined as gestational diabetes, gestational hypertension, pre-eclampsia, uterine rupture, placental abruption, placenta praevia, PROM and labour dystocia.

## DATA SOURCES AND SEARCH STRATEGY

We will conduct electronic searches in Ovid/MEDLINE, EMBASE, CINAHL, Scopus, Web of Science and PubMed databases, using a combination of medical subject headings (MeSH) and keywords related to IPI and pregnancy complications. We will include articles published from start of indexing until 12 February 2018 without any restriction on study type or geographic setting. A search strategy was developed (see [table 1](#) for search criteria and online Supplementary file 1 for detailed search strategy for each database).

The search strategy will be piloted across each database to improve the effectiveness of the final search. We will also check the reference list of primary studies that will be selected for full-text evaluation for additional potentially

**Table 1** Search criteria

Search terms	
Interpregnancy interval	Subject heading (MeSH) term: Birth interval Keywords: “‘birth interval’ or “‘birth spacing’ or “‘conception interval’ or “‘conception spacing’ or “‘delivery interval’ or “‘delivery spacing’ or “‘pregnancy interval’ or “‘pregnancy spacing’
Pregnancy complications	Subject heading (MeSH) term: ‘Pregnancy Complications’ Keywords: ‘obstetric complication*’ or ‘maternal complication*’ or ‘maternal morbidity*’ or ‘maternal outcome*’

relevant studies not identified by the electronic search. We will include studies published in peer-reviewed journals conducted with human populations and restricted to English language. Corresponding authors will be contacted to request information not presented in the manuscripts that are required for the review.

## ELIGIBILITY CRITERIA

### Inclusion criteria

The studies to be included in this review are required to fulfil two criteria.

*Study design criterion:* all observational studies evaluating the association between IPI and pregnancy complications.

*Exposure criterion:* studies that investigate IPI or birth interval as the primary exposure. *IPI* is defined as the length of time between the end of a pregnancy and the start of the next pregnancy. *Birth interval* is defined as the time elapsed between the end of one pregnancy and the end of the next pregnancy.

### Exclusion criteria

Studies will be excluded based on three criteria. (1) Non-primary studies: case series or reports, editorials, letters to the editor or reviews without original data. (2) Studies with insufficient information on adjusted effect (eg, unclear adjustment variable, missing CI estimates). (3) Studies that do not investigate IPI as a primary exposure.

### Study selection process and software

All unique studies identified from each electronic database will be imported into an *EndNote* library. For reproducibility and to expedite a future update of the review, this library will be published as online Supplementary data. Further screening of titles and abstracts will be accomplished by two independent investigators. Results will be stored using *Covidence*, a web-based software tool that (1) allows collation of search results, (2) screen abstracts and full text articles, (3) extract data from selected articles, (4) conduct risk of bias assessment and (5) resolve disagreements and export data. In accordance with Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA), a flow diagram will be used to report the screening process. From the set of studies screened by title and abstract, two reviewers will independently screen full-text articles based on the eligibility criteria. Any discrepancies between the two reviewers for studies that have been included or excluded will be discussed first, if an agreement cannot be reached, a third investigator will be consulted for moderation. The reason for excluding each study will also be recorded.

#### Risk of bias (quality) assessment

The quality of included studies will be assessed by two independent reviewers using The Newcastle-Ottawa Scale for assessing quality of cohort and cross-sectional studies.<sup>20</sup> Any disagreement which arises between the reviewers will be resolved through discussion with a third reviewer.

#### Data extraction

Data will be extracted from all included studies by two independent reviewers using a specifically developed data extraction form in line with the eligibility criteria and outcomes of interest. For each study, the following data will be extracted (1) author names, (2) publication year, (3) study period, (4) geographic location, (5) World Bank income category (at the time of publication), (6) study design, (7) sample size, (8) exposure, (9) outcome measure of interest, (10) adjustment or matching variables, (11) effect size and (12) response rate (where indicated).

#### Data synthesis and analysis

The final review will include data presented in summary tables and a narrative synthesis to describe the variables listed in the data extraction section. Where data permit, meta-analyses will be performed for individual pregnancy complications. We will apply random effects meta-analysis using the generic inverse variance method to explore the association between IPIs and pregnancy complications.<sup>21 22</sup> We will calculate pooled odds ratio (OR) from all studies that provided adjusted OR or risk ratio with 95% CIs for each pregnancy complication (outcome of interest). Egger's weighted regression test will be used to assess publication bias.<sup>23</sup> The  $I^2$  statistic will be reported as a measure of heterogeneity between studies.<sup>24</sup> Where meta-analysis is not possible, we will present data without quantitatively synthesising it. If the same data are presented in multiple studies, then those providing the most information will be considered.

#### Subgroup analyses

Subgroup analyses by country categories based on World Bank income group (high-income countries vs low and middle-income countries) will be performed.

#### Confidence in cumulative evidence

The quality of the findings on each outcome of interest across studies will be assessed using Grading of Recommendations, Assessment, Development and Evaluations

(GRADE) guidelines, which are developed by the GRADE Working Group.<sup>25</sup> The GRADE approach will allow us to determine the quality of the evidence of each outcome. The GRADE system classifies the quality of evidence as very low (*very uncertain effect estimates*), low (*further research will likely change the effect estimate*), moderate (*further research may change the estimate and our confidence in it*) or high (*further research is very unlikely to change our confidence in the estimate of effect*).

#### Patient and public involvement

Members of the community *Healthy Pregnancies Consumer Reference Group* will provide community and consumer perspectives to this study. This group will provide an insight into issues that affect their pregnancy planning decisions, contextualise results and provide participant experience.

#### Ethics and dissemination

Formal ethical approval is not required as primary data will not be collected. This protocol adheres to the PRISMA protocols guidelines.<sup>26</sup> In addition, the findings of the systematic review will be reported according to the PRISMA statement.<sup>27</sup>

#### Review registration

This review has been registered with International Prospective Register for Systematic Reviews (PROSPERO) under the identification code: CRD42018088578.

#### Updates to study protocol

If any updates to the study protocol are required, these will be listed and included as supplementary information along with a final manuscript and updated on the PROSPERO register.

## DISCUSSION

Families want to know the best time at which they conceive their next child in order to have a safer pregnancy and healthy baby. Clinicians need evidence-based recommendations to provide advice on the optimal IPI leading to fewer maternal and perinatal complications. For planned pregnancies, IPI is modifiable, and such recommendations may therefore be useful for preventing adverse maternal/pregnancy outcomes. The current WHO recommendations, which suggest that women wait at least 2 years after delivering a live birth,<sup>2</sup> were based on a review of observational studies predominantly in low-income and middle-income populations, which may not be generalisable to high-income countries. Context specific and updated evidence is warranted to clarify whether the evidence of studies investigated the effect of IPI on pregnancy complications is sufficient for decision-making.

This will be a comprehensive systematic review investigating the effect of IPI on pregnancy complications. Previous reviews have been limited to few maternal outcome of interest<sup>15</sup> or have not included results from studies published in the last 10 years.<sup>1</sup> A systematic review

investigating effect of IPI on pregnancy complications is now warranted. Systematic documentation and synthesising of literature on the effect of IPI on various pregnancy complications will be important to set and revise evidence-based guidelines for IPIs. By updating the current state of knowledge in IPI research, this review will provide a basis for guiding future studies and future global policies for family planning.

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**Contributors** ATG, AR, GP and EM conceived the idea, planned and designed the study protocol. ATG wrote the first draft. DF, SB and LM contributed to the development of the protocol and manuscript. All authors contributed to the initial question development, search strategy, study selection criteria and have approved and contributed to the final written manuscript.

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**Competing interests** None declared.

**Patient consent** Not required.

**Provenance and peer review** Not commissioned; peer reviewed for ethical and funding approval prior to submission.

**Data sharing statement** Supporting data can be found at the International prospective Register of Systematic Reviews (PROSPERO) website, with registration number CRD42018088578.

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