Interpregnancy interval following miscarriage and adverse pregnancy outcomes: Systematic Review and meta-analysis

Running Title: Optimum interpregnancy interval after miscarriage

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Abstract

Background: A short interpregnancy interval (IPI) following a delivery is believed to be associated with adverse outcomes in the next pregnancy. The optimum IPI following miscarriage is controversial. Based on a single large scale study in Latin and South America, the World Health Organization recommends delaying pregnancy for 6 months after a miscarriage to achieve optimal outcomes in the next pregnancy.

Objective and rationale: Our aim was to determine if a short IPI (<6months) following miscarriage is associated with adverse outcomes in the next pregnancy.

Search methods: Studies were retrieved from MEDLINE, Embase and Pubmed, with no time and language restrictions. The search strategy used a combination of Medical Subject Headings terms for miscarriage, IPI and adverse outcomes. Bibliographies of the retrieved articles were also searched by hand. All studies including women with at least one miscarriage, comparing subsequent adverse pregnancy outcomes for IPIs of less than and more than 6 months were included. Two independent reviewers screened titles and abstracts for inclusion. Characteristics of the studies were extracted and quality assessed using Critical Appraisal Skills Programme criteria. A systematic review and meta-analysis were conducted to compare short (<6 months) versus long (>6 months) IPI following miscarriage in terms of risk of further miscarriage, preterm birth, stillbirth, pre-eclampsia and low birthweight babies in the subsequent pregnancy. Review Manager 5.3 was used for conducting meta-analyses.

Outcomes: Sixteen studies including 1043840 women were included in the systematic review and data from 10 of these were included in one or more meta-analyses (977972 women).

With an IPI of less than 6 months, the overall risk of further miscarriage (Risk ratio (RR) (AUTHOR: correct?) 0.82 95%CI 0.78, 0.86) and preterm delivery (RR 0.79 95%CI 0.75, 0.83) were significantly reduced. The pooled risks of stillbirth (RR 0.88 95% CI 0.76, 1.02);

low birthweight (RR 1.05 95% CI 0.48, 2.29) and pre-eclampsia (RR 0.95 95% CI 0.88, 1.02) were not affected by IPI. Similar findings were obtained in subgroup analyses when IPI of <6months was compared with IPI of 6 to 12 months and >12 months.

Wider implications: This is the first systematic review and meta-analysis providing clear evidence that an IPI of less than 6 months following miscarriage is not associated with adverse outcomes in the next pregnancy. This information may be used to revise current guidance.

Key words: Interpregnancy interval, miscarriage, recurrent miscarriage, pregnancy outcomes, preterm birth, live birth, stillbirth, low birthweight, preeclampsia

Introduction

Miscarriage is a relatively common occurrence, affecting 10-15% of all pregnancies in the UK (Bhattacharya et al., 2008). It is defined as any pregnancy loss that occurs in the first 24 weeks (Bhattacharya et al., 2008), although the gestational week cut off varies according to availability of neonatal care. Loss of a pregnancy through miscarriage is associated not only with psychological distress but may also affect the outcomes of the subsequent pregnancy resulting in further miscarriage, pre-eclampsia and preterm delivery (Bhattacharya et al., 2008). Birth spacing after an initial miscarriage may help mitigate some of these risks. The time between the end of a pregnancy and the start of another one is defined as the interpregnancy interval (IPI) (Bentolila et al., 2013). The optimum IPI after a live birth has been reported to be 18-23 months, for better maternal and perinatal outcomes in the next pregnancy (Conde-Agudelo et al., 2006) In their meta-analysis of observational studies, Conde Agudelo et al (2006) found J shaped associations between IPI following a live birth and adverse outcomes in the subsequent pregnancy. Intervals shorter than 20 months and longer than 60 months conferred the highest risk of preterm birth, low birthweight and small for gestational age; while intervals shorter than 6 months and longer than 50 months were associated with the highest risk of perinatal deaths. The optimum IPI after a miscarriage is, however, controversial. Some clinicians advise couples not to delay conceiving the next pregnancy, as an increasing IPI after a miscarriage does not appear to improve birth outcomes (Basso et al., 1998; Goldstein et al., 2002; Love et al., 2010). Others suggest delaying pregnancy for at least 18 months based on the optimum IPI after a live birth (Conde-Agudelo et al., 2006). The World Health Organization (WHO) guidelines recommend waiting for at least 6 months before trying to conceive again after a miscarriage (WHO, 2005). These guidelines were based on a single multicentre study in Latin and South America, which found that an IPI of less than 6 months following miscarriage was associated with adverse outcomes in the next pregnancy (Conde Agudelo, 2004). This study however, was unable to distinguish between miscarriage and induced abortion and this may have

affected their findings. As increased maternal age is independently associated with increased risk of miscarriage (Aref-Adib et al., 2008), delaying conception after a miscarriage may further increase this risk**.** We therefore performed a systematic review with meta-analyses looking at the relationship between a short IPI (less than 6 months) compared to 6 months or more following a miscarriage and adverse outcomes in the next pregnancy.

Methods

Ethical Approval: As this study was a systematic review and meta-analysis of aggregated published data, formal ethical approval was not required.

Review protocol: At first a specific protocol was designed where the review question was formulated using the Population, Exposure, Comparison and Outcome (PECO) (AUTHOR: please provide full form of PICO. Thank you.) format. The population (P) of interest was women with at least one pregnancy following a miscarriage, exposure (E) was IPI of less than 6 months compared (C) to IPI of 6 months or more. The pre-specified outcomes (O) of interest were further miscarriage, preterm birth, stillbirth, pre-eclampsia and low birthweight in the pregnancy following miscarriage. All types of study design were assessed for eligibility. The criteria used to identify, include and exclude studies and the methods for analysing data were all derived from this format and agreed *a priori* in the review protocol. The review was conducted and reported according to the guidelines of the Meta-analysis of Observational studies in Epidemiology group (MOOSE checklist). The protocol was registered with PROSPERO (registration number CRD42016038424).

Literature search: A search strategy was initially developed in Ovid Medline then modified and run in other databases - PubMed (U.S. National Library of Medicine), Embase (Elsevier) and Scopus. The search strategy used a combination of Medical Subject Headings (MeSH) terms for miscarriage, interpregnancy interval and adverse outcomes. The terms for miscarriage were: miscarriages, abortion, spontaneous abortion, early pregnancy loss. Other terms for interpregnancy interval were interconception interval, time to birth, birth spacing

and birth interval. Terms for adverse outcomes were pregnancy outcomes, adverse outcomes. A further search was conducted using specific terms for interpregnancy interval: long IPI, short IPI, more than 6 months IPI, less than 6 months IPI. A specific search was also conducted for the names of each adverse outcome, these terms were: further miscarriage, pregnancy loss, stillbirth, preterm birth, low birth weight, preeclampsia. These search terms were combined using Boolean operators "AND" or "OR" as appropriate. No time or language restrictions were applied to the search strategy. Two reviewers (CK and SL) independently ran the searches.

Review methods: The titles and abstracts of the articles identified by this search were independently screened by two reviewers (CK and SL) for inclusion in the review and the full texts of those that appeared relevant were retrieved. Bibliographies of the retrieved articles were also searched by hand. Where there was inadequate information in the published article, authors were contacted to request additional data.

All the retrieved full text articles were then assessed for inclusion in the review using the predefined exclusion and inclusion criteria.

The criteria determining whether an article was going to be included were:

- if the populations studied were women with at least one miscarriage. The studies with women with no miscarriage but just live births or induced abortions were excluded.
- if the studies used IPI as exposure. Studies were excluded if they did not include IPI or the women did not have any further pregnancies.
- if they had studied IPIs for less and more than 6 months. Studies were excluded if they did not have comparison groups or did not report findings for IPIs of less than 6 months. Nevertheless authors were contacted to see if they could provide appropriate data if the range of IPI was inconsistent with this inclusion criterion.
- if the studies had the outcomes that were relevant to this review. Outcomes were broadly categorised into primary and secondary outcomes based on frequency and

consistency of association reported in the literature, biological plausibility and clinical importance. Primary outcomes were defined as further miscarriage (less than 24 weeks of gestation) and preterm delivery (delivery before 37 weeks of gestation). Secondary outcomes were live birth, stillbirth, pre-eclampsia, and low birthweight. Studies were included if they had adverse outcomes in the next pregnancy and excluded if they only reported adverse outcomes in the same pregnancy.

Studies were also excluded if they were case reports, reviews or editorials.

Quality assessment and risk of bias: Once the potentially eligible articles were retrieved, they were assessed for methodological quality using the CASP (Critical Appraisal Skills Programme) checklist for cohort studies (Critical Appraisal Skills Programme (CASP), 2016). The following were extracted from each included article: titles, authors' names, the type of study, characteristics of the population studied, the setting of the study (the geographical location), the outcomes studied, the measured exposure IPI).

Statistical analysis: Meta-analysis was performed where appropriate using the software Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Copenhagen, Denmark.). Data were entered for each outcome if there were at least two studies addressing that outcome. The raw numbers for each outcome in each group of IPI (≥6 months or <6 months) as reported in the primary studies were entered in the software to calculate the crude risk ratio (RR) and the 95% CI using ≥6 months as the reference category. These were then weighted and pooled to produce forest plots and pooled RRs with 95%CI. Statistical heterogeneity was assessed using the I^2 statistic. Where I^2 was more than 50% signifying moderate to large statistical heterogeneity, a random effects model was used.

If a study varied significantly in terms of methodology or findings from all other included studies, we performed a sensitivity analysis excluding those studies from the meta-analysis.

In subgroup analyses, we split the comparator group of >6 months into 6–12 months and >12 months for the primary outcomes of further miscarriage and preterm birth.

Results

Figure 1 shows the process for the search and identification of studies. The bibliographic searches identified 151 publications and 18 others were found from a hand search of the references. Of these, 38 publications were considered relevant and the full text reviewed for inclusion. Of these, 13 cohort studies (Bentolila et al., 2013; Basso et al., 1998; Goldstein et al., 2002; Love et al., 2010; Davanzo et al., 2012; Buchmayer et al., 2004; Davanzo et al., 2007; Conde-Agudelo et al., 2004; Wyss et al., 1994; El Behery et al., 2013; Sapra et al., 2014; Cox et al., 2010; Morgan-Ortiz et al., 2010) and 3 randomized control trials (Makhlouf et al., 2014; Kaandorp et al., 2014; Wong et al., 2015) met the inclusion criteria. However 6 of these articles had insufficient data for inclusion in meta-analysis; the authors of these papers were contacted but were unable to provide additional data. Therefore, 10 (Bentolila et al., 2013; Love et al., 2010; Davanzo et al., 2012; Wong et al., 2015; Buchmayer et al., 2004; Davanzo et al., 2007; Makhlouf et al., 2014; Conde-Agudelo et al., 2004; Wyss et al., 1994; Morgan-Ortiz et al., 2010) studies were included in the meta-analyses.

Table 1 shows the characteristics of the included studies (13 cohort and 3 RCTs) along with their quality assessment scores. The authors also carried out a secondary cohort analysis of the women in the three RCTs to look at the effect of a short IPI after a previous loss (Kaandorp et al, 2014; Makhlouf et al, 2014 and Wong et al., 2015). Out of the 16 studies, 4 were set in the USA (Goldstein et al., 2002; Wong et al., 2015; Makhlouf et al., 2014; Sapra et al., 2014), two in Bangladesh (Davanzo et al., 2012; Davanzo et al., 2007), two in the Netherlands (Kaandorp et al., 2014; Cox et al., 2010) and one each in Scotland (Love et al., 2010), Denmark (Basso et al., 1998), Sweden (Buchmayer et al., 2004), Egypt (El Behery et al., 2013) Israel (Bentolila et al., 2013), Switzerland (Wyss et al., 1994), Uruguay (Conde-Agudelo et al., 2004) and Spain (Morgan-Ortiz et al., 2010). Most studies looked at IPI in

months, while two studies looked at IPI in terms of menstrual cycles in days (Goldstein et al., 2002; Sapra et al., 2014). All the studies used a population of women with one miscarriage or recurrent miscarriages.

Eight studies provided data on preterm birth (Bentolila et al., 2013; Love et al., 2010; Wong et al., 2015; Buchmayer et al., 2004; Makhlouf et al., 2014; Conde-Agudelo et al., 2004; Wyss et al., 1994; Morgan-Ortiz et al., 2010), seven on further miscarriage (Bentolila et al., 2013; Love et al., 2010; Davanzo et al., 2012; Wong et al., 2015; Davanzo et al., 2007; Wyss et al., 1994; Morgan-Ortiz et al., 2010) four on live births (Love et al., 2010; Davanzo et al., 2012; Wong et al., 2015; Davanzo et al., 2007), four on stillbirths (Love et al., 2010; Davanzo et al., 2012; Wong et al., 2015; Davanzo et al., 2007), five on pre-eclampsia (Bentolila et al., 2013; Love et al., 2010; Wong et al., 2015; Makhlouf et al., 2014; Conde-Agudelo et al., 2004) and four on low birthweight (Bentolila et al., 2013; Love et al., 2010; Makhlouf et al., 2014; Conde-Agudelo et al., 2004). The study by Conde-Agudelo et al (Conde-Agudelo et al., 2004) did not distinguish between spontaneous and induced abortions and a sensitivity analysis was performed including and excluding this study. The average quality assessment score using CASP criteria was 9.4 out of 11, therefore all the included studies were of good quality with low risk of bias. Publication bias was investigated using a funnel plot for the outcome - further miscarriage but showed no appreciable evidence of this bias. (Please see supplementary figure 1)

Further miscarriage

Seven of the ten studies provided data on further miscarriage after a previous miscarriage. The risk of having a further miscarriage with IPI of less than 6 months was significantly reduced when compared to IPI of more than 6 months, with a pooled RR (95% CI) of 0.82 (0.78, 0.86) (Figure II A). Compared to an IPI of 6–12 months, IPI of <6 months reduced the risk of further miscarriage (pooled RR 0.82, 95% CI 0.77, 0.88). Similarly this risk was further reduced (pooled RR 0.78, 95% CI 0.74, 0.83) when compared with IPI >12 months.

Preterm birth

Out of the ten studies included in meta-analysis, eight reported on preterm deliveries. We performed a meta-analysis including and excluding the study by Conde Agudelo et al (2004). The meta-analysis including the study by Conde Agudelo et al (2004) resulted in a pooled RR of 0.93(95% CI 0.58, 1.48) (Fig IIB). The incidence of preterm deliveries was significantly lower (P <0.01) when women with IPI of less than 6 months were compared to those with an IPI of more than 6 months: pooled RR (95% CI) of 0.79 (0.75, 0.83) (Figure IIB) when the study by Conde Agudelo et al (2004) was excluded. There was no significant increase in the risk of preterm birth when compared with IPI of 6 to 12 months (pooled RR 1.10, 95% CI 0.64, 1.89) or with IPI of >12 months (pooled RR 1.06, 95% CI 0.57, 1.97). The study by Conde Agudelo et al (2004) was included in the latter two meta-analyses.

Live birth

Four studies presented data on live births after a miscarriage. Live births were observed to be significantly higher when women had an IPI of less than 6 months after a miscarriage (P<0.01), 40% higher compared to an IPI of 6 months or more, RR of (95% CI) 1.06 (1.01, 1.11) (Figure IIC).

Stillbirth

The reported risk of stillbirths in women after a miscarriage was not significantly different in the two IPI groups (P=0.09) RR (95% CI) of 0.88 (0.76, 1.02). The risk varied from 1.56 to 0.71 across the four studies included in the meta-analysis (Figure IID).

Low birthweight

Four studies presented data on low birthweight, 3 of the studies defined low birthweight as less than 2500 g (Bentolila et al., 2013; Love et al., 2010; Conde-Agudelo et al., 2004) and 1 as less than the fifth percentile for gestational age adjusted by sex and race (Makhlouf et al., 2014). The overall risk of having low birthweight babies after a miscarriage was not

significantly different in women with an IPI of less than 6 months (P=0.07), compared to women with an IPI of 6 months or more including the study by Conde Agudelo et al (2004) RR (95% CI) of 1.05(0.48, 2.29) (Fig. IIE). When this study was excluded, the risk of low birthweight was significantly lower with IPI of <6 months (pooled RR 0.74 95% CI 0.68, 0.81) (Figure IIE lower panel).

Pre-eclampsia

The rate of pre-eclampsia did not appear to differ in women with IPI of less than 6 months after a miscarriage compared to IPI ≥6 months, including the study by Conde Agudelo et al., 2004 pooled RR (95% CI) of 0.95 (0.88, 1.02) (Figure II F) and excluding the study 1.00 (0.90, 1.12) (Figure IIF lower panel). Five of the ten studies provided data on pre-eclampsia.

Discussion

Birth spacing is an important element of reproductive counselling. Couples experiencing a miscarriage need to know the optimal time to conceive another pregnancy in order to have the best possible outcomes. In this systematic review, we evaluated 6 different outcomes and found that an IPI of less than 6 months following a miscarriage was associated with lower risks of having a further miscarriage and preterm delivery, and increased odds of having live births. There were no differences in the risks of stillbirth, pre-eclampsia and low birthweight babies between an IPI of less than 6 months and of 6 months or more. Based on the published evidence from ten studies we can therefore conclude that delaying a pregnancy for more than 6 months after a miscarriage is unnecessary as a short IPI (less than 6 months) results in no worse pregnancy outcomes but may also be associated with better outcomes in terms of a lower risk of further miscarriage and preterm birth and increased chance of live birth in the next pregnancy.

This systematic review was carried out in compliance with the criteria in the MOOSE checklist. At first a focussed review question was framed using the PECO format, from which a robust search strategy and inclusion and exclusion criteria were developed. The studies

were carefully assessed for quality independently by two reviewers and data extracted for meta-analyses. The meta-analysis in this review included 10 studies. The study by Conde-Agudelo et al., 2004 provided outcome data on further miscarriage, preterm delivery, low birthweight and pre-eclampsia. While this was a large retrospective study on which the WHO guidelines for delaying pregnancy for at least 6 months (WHO, 2005) is based, it did not differentiate between induced and spontaneous abortions and used data from many countries where induced abortion is illegal (Conde-Agudelo et al., 2004). Therefore the conclusions from this study should be interpreted in context. The meta-analyses were repeated with and without this study in sensitivity analyses. The exclusion of this study had large effects on the pooled outcome estimates. In several cases, such as preterm birth, a shorter IPI was associated with more favourable outcomes.

Meta-analyses and systematic reviews can be limited by a number of factors. Original data collection varied across the different studies as some used the mother's recall of the previous pregnancies while others used information from databases. Thus quality of the original data is a limiting factor. In addition, studies varied in their definition of certain outcomes such as miscarriage. While some studies made distinctions between women with spontaneous and induced abortions, others could not - possibly due to legal constraints and religious and cultural stigmas associated with induced abortions. Another potential bias is publication bias, and although the literature search was rigorous we were unable to search unpublished studies, which may affect our results. We investigated this possibility using a funnel plot which did not demonstrate any appreciable publication bias for the outcome of further miscarriage but may have been present for some of the secondary outcomes with fewer publications. Furthermore confidence in the results could be limited due to the small number of studies used in the meta-analyses. A number of factors are associated with pregnancy outcomes, including age, ethnicity, social class, smoking, alcohol, BMI, and previous obstetric history, however other than maternal age, the studies also varied in addressing potential confounders. Failure to address all the potential confounders in the

primary studies included in this review could be due to the fact that they were not recorded in the databases, or either not measured or poorly measured. Thus this can be recognised as a potential limitation in this study as it can lead to over or under estimated results. Despite this, a consistent effect was reported by all the studies conducted in a variety of countries and settings, which leads us to believe that these associations are likely to exist.

The results of this systematic review are consistent with other studies (Basso et al., 1998; Goldstein et al., 2002; El Behery et al., 2013) that could not be included in this meta-analysis as they did not have appropriate data. The study by El Behery et al (2013) shows that women conceiving within 6 months of a miscarriage had good reproductive outcomes and a reduced incidence of complications, and they noted that live births were highest when conceiving within 6 months (79.31%) compared to conceiving after 12 months (71.6%). However they did not focus on an IPI of more than 6 months, but looked only at less than 6 months IPI and more than 12 months IPI hence this study could not be included in the main meta-analysis but only in the subgroup analysis comparing IPI of less than 6 months with that of more than 12 months (El Behery et al., 2013). Studies by Basso et al (Basso et al., 1998) and Goldstein et al (Goldstein et al., 2002) show that there are no adverse outcomes associated with short IPIs but also that adverse outcomes increase as IPI increases (Basso et al., 1998). However they did not use the same IPI groups as this systematic review therefore could not contribute towards the meta-analyses.

In their systematic review of mechanisms underpinning short and long IPI with adverse pregnancy outcomes, Conde Agudelo et al., 2012 found evidence to support hypotheses of maternal nutritional depletion, folate depletion, cervical insufficiency, vertical transmission of infections and abnormal remodelling of endometrial blood vessels as possible explanations for the association of adverse outcomes with short IPI. Women's natural decline in reproductive capacity with age was the only hypothesis proposed to explain the association between long IPIs and adverse outcomes. (Conde Agudelo et al, 2012). In cases where the IPI starts with a miscarriage, the woman’s body may behave differently to that after a live

birth. For example, the nutritional depletion or folate depletion hypothesis suggests that from the fifth month of pregnancy until a prolonged time after delivery, the stores of maternal nutrients, such as folate, remain low leading to folate insufficiency in women with a short IPI after a live or stillbirth. However after a miscarriage, there is a very small burden on the folate reserve and thus miscarriage is not very likely to lead to folate deficiency in the postpartum period. This could explain the reduced risk of adverse outcomes in a short IPI after a miscarriage (Smits and Essed, 2001). In support of this hypothesis, there is evidence to suggest that late miscarriages (after 12 weeks of gestation) are associated with worse outcomes in the subsequent pregnancy (Edlow et al., 2007). In addition, most women who attempt another pregnancy soon after a miscarriage are likely to be motivated to take better care of their health and consequently result in better pregnancy outcomes (Davanzo et al., 2007). Another plausible reason may be that those who conceive soon after a miscarriage are naturally more fertile and consequently have better pregnancy outcomes.

This is the first systematic evidence synthesis to assess the effect of short versus long IPI and based on the available evidence we can conclude that a short IPI (less than 6 months) following miscarriage is not associated with adverse outcomes in the subsequent pregnancy. Couples wishing to conceive after a miscarriage can be counselled that delaying pregnancy does not necessarily improve outcomes. Further research needs to look at an IPI of less than 3 months to determine an optimum cut off, if there is one. Individual patient data meta-analysis can offer opportunities to study small subgroups and/or stratify by other risk factors to determine a personalised optimum IPI after miscarriage.

Conclusion

The results of this systematic review and meta-analyses show that an IPI of less than 6 months is associated with no increase in the risks of adverse outcomes in the pregnancy following miscarriage compared to delaying pregnancy for at least 6 months. In fact, there is some evidence to suggest that chances of having a live birth in the subsequent pregnancy

are increased with an IPI of less than 6 months. There is now ample evidence to suggest that delaying a pregnancy following a miscarriage is not beneficial and unless there are specific reasons for delay couples should be advised to try for another pregnancy as soon as they feel ready.

Authors' roles: CK conducted the initial literature searches, reviewed the included papers, conducted the meta-analyses and wrote the first draft. SL repeated the searches, quality assessed the included studies and commented on the draft. SB designed the review question, developed the protocol, supervised CK and SL.

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Conflict of Interest:

The authors declare that they have no conflict of interest.

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AUTHOR: please would you format the references according to journal style, in particular make the journal italic text, and the volume number bold? Thank you.

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Figure legends

Figure I Flow diagram of study identification and selection process for systematic review of the association between interpgnancy interval following miscarriage and subsequent pregnancy outcomes

Figure II Forest plots presenting the association of interpregnancy interval following miscarriage with subsequent pregnancy outcomes

Figure II A Forest plot presenting the association of interpregnancy intervals following miscarriage with further miscarriage

Figure II B. Forest plot presenting the association of interpregnancy intervals following miscarriage with subsequent preterm birth

Figure II C. Forest plot presenting the association of interpregnancy intervals following miscarriage with subsequent live birth

Figure II D. Forest plot presenting the association of interpregnancy intervals following miscarriage with subsequent stillbirth

Figure II E. Forest plot presenting the association of interpregnancy intervals following miscarriage with subsequent delivery of low birthweight babies

Figure II F. Forest plot presenting the association of interpregnancy intervals following miscarriage with subsequent pre-eclampsia

Supplementary Figure I Funnel plot examining publication bias for the association between interpregnancy interval and further miscarriage

Table 1 Characteristics and quality of 16 studies included in a systematic review on interpregnancy interval following miscarriage and adverse pregnancy outcomes.

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Reference	Design	Setting	Population	Exposure (IPI)	Outcome	Confounders	Q A Score
Wong et al., 2015	RCT/ analysed as cohort	4 clinical trial sites in USA	Women with ≥ 1 previous miscarriage	3 monthly intervals 0 to>12	Live birth; pregnancy loss	Age, BMI, race, gestational age of previous loss	11
Kaandorp et al.,2014	RCT/cohort	ALIFE trial Netherlands (2004 – 2009)	Women with unexplained recurrent miscarriage	6, 12 and 24 months	Weeks to conception; time to live birth	Age, BMI, no. of miscarriages, intervention, previous live birth, factor V Leiden mutation	7
Makhlouf et al., 2014	RCT/ cohort	Eunice Kennedy Shriver National Institute RCT (2003 – 2008)	Women with previous miscarriage	<6 , 6-12, >12 months	Preterm birth, pre-eclampsia, fetal/ neonatal death, birthweight	Age, BMI, race, smoking, education, marital status	11
Sapra et al., 2014	cohort	Michigan & Texas USA (2005 – 2009)	Women with miscarriage	No of menstrual cycles	pregnancy	Age, BMI, smoking, caffeine and alcohol intake	8
Bentolila et al., 2013	cohort	RPL clinic in the Soroka University Medical Center, Israel	Women with 2 or more consecutive miscarriage	< 6 and > 6 months	Adverse outcomes in the next pregnancy	Age, ethnicity	11
DaVanzo et al., 2012	cohort	Matlab DHSS Bangladesh (1977 – 2008)	Women with miscarriage	3 and 6 month intervals	Miscarriage, termination; stillbirth; early, late and post neonatal mortality	Age, education, geographic area, gravidity, calendar year	10
El Behery et al.,2013	cohort	Zagazig & Suez Canal University Hospitals (2009 to 2012)	Women with 1st pregnancy miscarriage	<6 months and >12 months	Miscarriage, ectopic, termination, stillbirth, live birth, pre-eclampsia, placenta	Age, BMI, smoking, voluntary/ involuntary IPI,	10

Reference	Design	Setting	Population	Exposure (IPI)	Outcome	Confounders	Q A Score
					praevia, abruption, PPH, low birthweight, preterm delivery	gynaecological history	
Love et al., 2010	cohort	Scotland (1981 – 2000)	Women with 1st pregnancy miscarriage	6 monthly intervals from <6 to >24	Miscarriage, ectopic, live birth, stillbirth; pre-eclampsia, placenta praevia, placental abruption, induction of labour, caesarean, preterm, low birthweight	Age, social class, smoking, calendar year	9
Morgan-Ortiz et al., 2010	cohort	Mexico	Women with early pregnancy loss in last pregnancy	</> 6 months	Further miscarriage, preterm birth and perinatal outcomes: agpar <7	None	-
Cox et al., 2010	cohort	38 fertility centres in the Netherlands	Women with ≥ 1 previous miscarriage	6 – 18 months	Spontaneous ongoing pregnancy	Age, duration of subfertility, sperm motility, post-coital test	8
DaVanzo et al.,2007	cohort	Matlab, Bangladesh (1982 – 2002)	All pregnancies including miscarriage	<6, 6 – 14, 15 – 26, 27 – 50, 51 – 74 and >74 months	Live birth, stillbirth, miscarriage	Age, parity, education, household space, religion, planned pregnancy, calendar year	9
Conde Agudelo et al.,2004	cohort	Latin & South America (1985 – 2002)	Women delivering singleton with previous history of abortion (spontaneous or induced).	IPI (in months): < 2 ,3-5, 6-11,12-17, 18-23, 24-59, >60	Multiple adverse pregnancy outcomes	Age, parity, education, marital status, smoking BMI, gestational weight gain, geographic area,	7

Reference	Design	Setting	Population	Exposure (IPI)	Outcome	Confounders	Q A Score
						hospital type, calendar year	
Buchmayer et al., 2004	cohort	Sweden (1987 – 2000)	Women with previous pregnancy loss	0 -3, 3-6, 6-12 and >12 intervals	Preterm delivery	Age, relationship with father , smoking, mother's birth country, calendar year	9
Goldstein et al., 2002	cohort	University of California, San Francisco, USA	Women with 1 previous miscarriage	0 or 2 menstrual cycles, 100 days	Preterm delivery, caesarean section	Age, ethnicity, education, parity, gravidity, Rh status, prior abortions/ ectopic	7
Basso et al., 1997	cohort	Denmark (1980 – 1992)	Women with live birth following miscarriage	Monthly IPI	Preterm delivery, low birthweight, growth retardation	Age, social class, change of social status	10
Wyss et al., 1994	cohort	Women with 1 previous miscarriage	University Hospital Zurich, Switzerland (1986 – 1991)	< 90 days >90 days	Subsequent miscarriage, preterm birth	Age and parity (previous livebirth)	8

481 IPI:interpregnancy interval, QA: quality assessment, Rh: rhesus, PPH : Postpartum Haemorrhage

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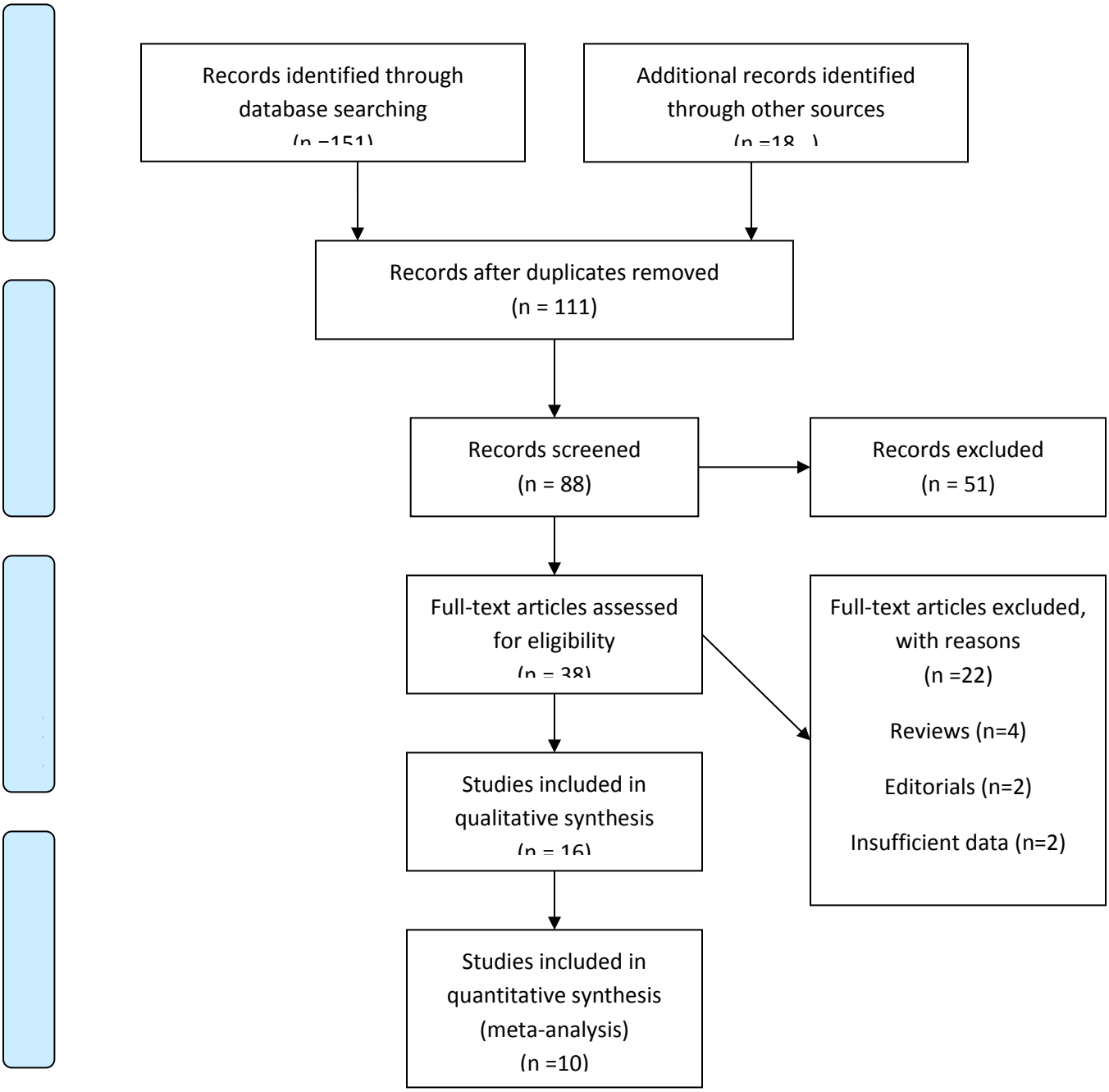
Figure I. Flow diagram of study identification and selection process for systematic review of the association between interpgnancy interval following miscarriage and subsequent pregnancy outcomes



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

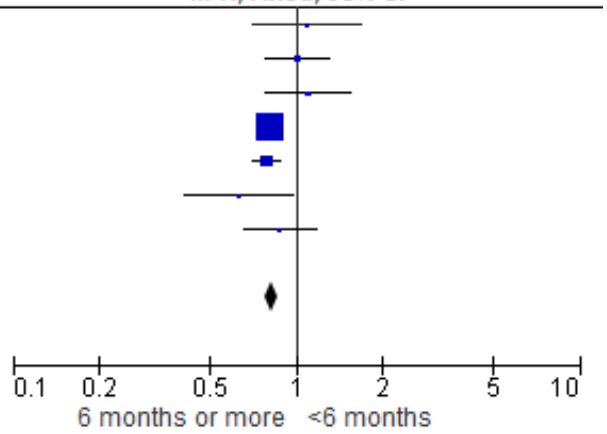
For more information, visit www.prisma-statement.org.

Figure II Forest plots of selected outcomes

A Further miscarriage

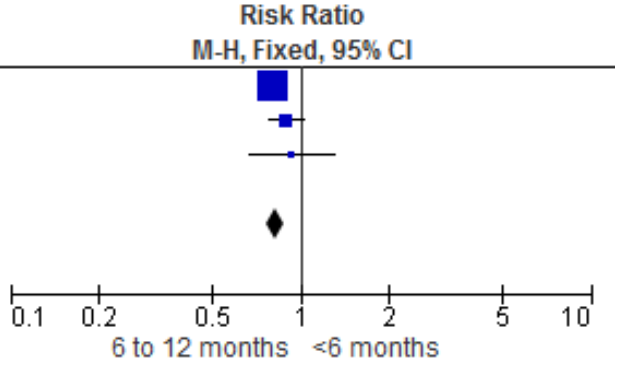
Study or Subgroup	Less than 6 months Events	Total	6 months or more Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Wyss 1994	91	443	19	101	1.1%	1.09 [0.70, 1.70]	1994
DaVanzo 2007	112	1366	95	1171	3.6%	1.01 [0.78, 1.31]	2007
Morgan-Ortiz 2010	42	286	76	572	1.8%	1.11 [0.78, 1.57]	2010
Love 2010	1308	12744	2311	18193	67.8%	0.81 [0.76, 0.86]	2010
DaVanzo 2012	422	4596	681	5839	21.4%	0.79 [0.70, 0.88]	2012
Bentolila 2013	21	113	63	212	1.6%	0.63 [0.40, 0.97]	2013
Wong 2015	96	445	57	232	2.7%	0.88 [0.66, 1.17]	2015
Total (95% CI)		**19993**		**26320**	**100.0%**	**0.82 [0.78, 0.86]**	
Total events	2092		3302				

Heterogeneity: Chi² = 9.22, df = 6 (P = 0.16); I² = 35%
Test for overall effect: Z = 7.51 (P < 0.00001)



Study or Subgroup	Less than 6 months Events	Total	6 to 12 months Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Love 2010	1308	12744	1004	7791	74.7%	0.80 [0.74, 0.86]	2010
DaVanzo 2012	422	4596	302	2920	22.1%	0.89 [0.77, 1.02]	2012
Wong 2015	96	445	36	155	3.2%	0.93 [0.66, 1.30]	2015
Total (95% CI)		**17785**		**10866**	**100.0%**	**0.82 [0.77, 0.88]**	
Total events	1826		1342				

Heterogeneity: Chi² = 2.30, df = 2 (P = 0.32); I² = 13%
Test for overall effect: Z = 5.83 (P < 0.00001)



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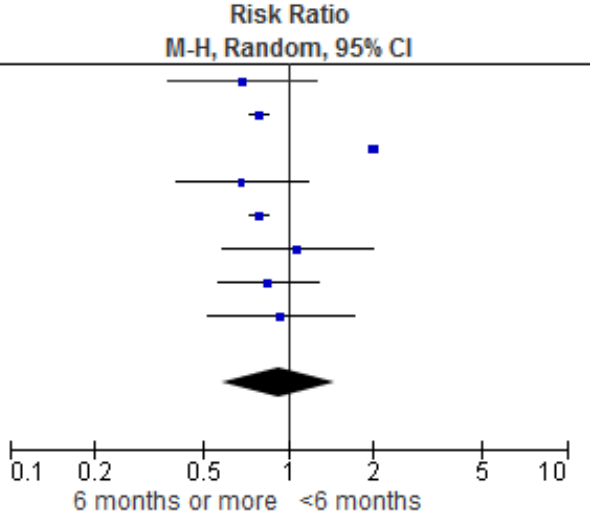
B Preterm Birth

Study or Subgroup	Less than 6 months Events	Total	6 months or more Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Wyss 1994	36	443	12	101	11.3%	0.68 [0.37, 1.27]	1994
Buchmayer 2003	1023	15451	1448	17128	13.9%	0.78 [0.73, 0.85]	2003
Conde Agudelo 2004	2466	11615	25842	246493	14.0%	2.03 [1.95, 2.10]	2004
Morgan-Ortiz 2010	16	286	47	572	11.7%	0.68 [0.39, 1.18]	2010
Love 2010	964	10856	1571	13977	13.9%	0.79 [0.73, 0.85]	2010
Bentolila 2013	14	92	21	149	11.2%	1.08 [0.58, 2.02]	2013
Makhlouf 2014	31	395	60	645	12.6%	0.84 [0.56, 1.28]	2014
Wong 2015	27	445	15	232	11.3%	0.94 [0.51, 1.73]	2015
Total (95% CI)		**39583**		**279297**	**100.0%**	**0.93 [0.58, 1.48]**	
Total events	4577		29016				

Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 869.52$, df = 7 ($P < 0.00001$); $I^2 = 99\%$

Test for overall effect: Z = 0.32 (P = 0.75)



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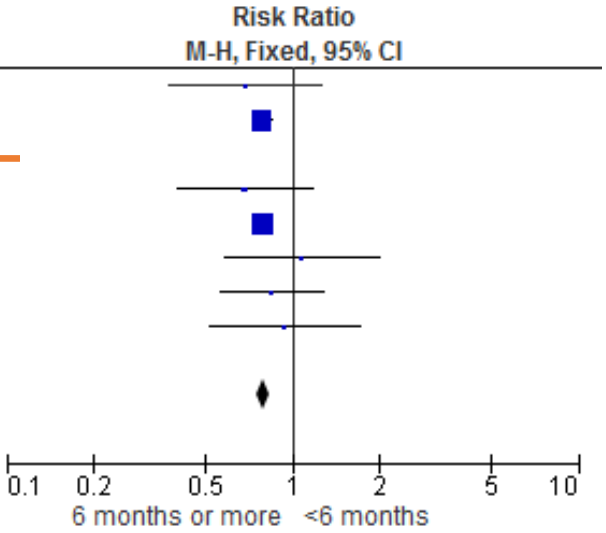
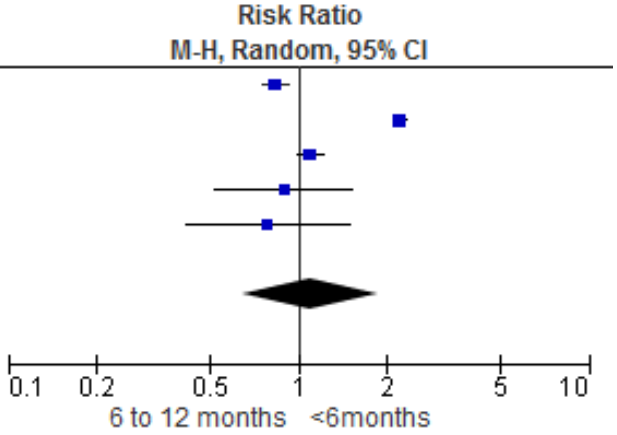
Study or Subgroup	Less than 6 months Events	Total	6 months or more Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Wyss 1994	36	443	12	101	0.7%	0.68 [0.37, 1.27]	1994
Buchmayer 2003	1023	15451	1448	17128	47.7%	0.78 [0.73, 0.85]	2003
~~Conde Agudelo 2004~~	~~2466~~	~~11615~~	~~25842~~	~~248433~~		~~Not estimable~~	~~2004~~
Morgan-Ortiz 2010	16	286	47	572	1.1%	0.68 [0.39, 1.18]	2010
Love 2010	964	10856	1571	13977	47.7%	0.79 [0.73, 0.85]	2010
Bentolila 2013	14	92	21	149	0.6%	1.08 [0.58, 2.02]	2013
Makhlouf 2014	31	395	60	645	1.6%	0.84 [0.56, 1.28]	2014
Wong 2015	27	445	15	232	0.7%	0.94 [0.51, 1.73]	2015
Total (95% CI)		**27968**		**32804**	**100.0%**	**0.79 [0.75, 0.83]**	
Total events	2111		3174				

Heterogeneity: Chi² = 1.90, df = 6 (P = 0.93); I² = 0%
Test for overall effect: Z = 8.82 (P < 0.00001)



Study or Subgroup	Less than 6 months Events	Total	6 to 12 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Buchmayer 2003	1023	15451	541	6792	21.8%	0.83 [0.75, 0.92]	2003
Conde Agudelo 2004	2466	11615	3752	39491	21.9%	2.23 [2.13, 2.34]	2004
Love 2010	964	10856	500	6154	21.8%	1.09 [0.99, 1.21]	2010
Makhlouf 2014	31	395	19	216	17.9%	0.89 [0.52, 1.54]	2014
Wong 2015	27	445	12	155	16.6%	0.78 [0.41, 1.51]	2015
Total (95% CI)		**38762**		**52808**	**100.0%**	**1.10 [0.64, 1.89]**	
Total events	4511		4824				

Heterogeneity: Tau² = 0.35; Chi² = 415.09, df = 4 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.34 (P = 0.73)



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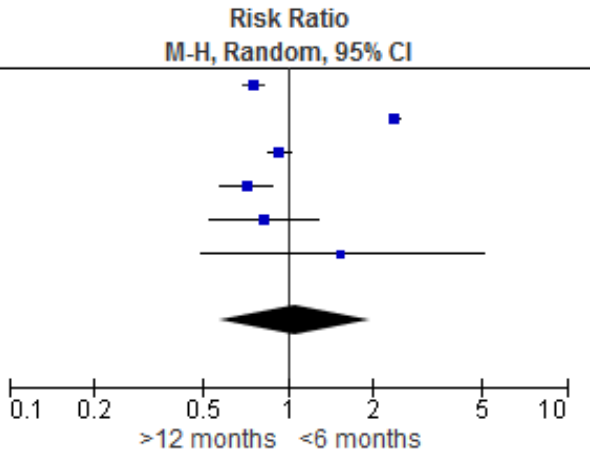
Study or Subgroup	Less than 6 months Events	Total	More than 12 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Buchmayer 2003	1023	15451	907	10336	18.1%	0.75 [0.69, 0.82]	2003
Conde Agudelo 2004	2466	11615	18113	207002	18.2%	2.43 [2.34, 2.52]	2004
Love 2010	964	10856	743	7823	18.1%	0.93 [0.85, 1.02]	2010
El Behery 2013	139	1944	162	1614	17.8%	0.71 [0.57, 0.88]	2013
Makhlouf 2014	31	395	41	429	16.6%	0.82 [0.53, 1.28]	2014
Wong 2015	27	445	3	77	11.1%	1.56 [0.48, 5.01]	2015
Total (95% CI)		**40706**		**227281**	**100.0%**	**1.06 [0.57, 1.97]**	
Total events	4650		19969				

Heterogeneity: $Tau^2 = 0.56$; $Chi^2 = 971.00$, $df = 5$ ($P < 0.00001$); $I^2 = 99\%$

Test for overall effect: $Z = 0.17$ ($P = 0.87$)



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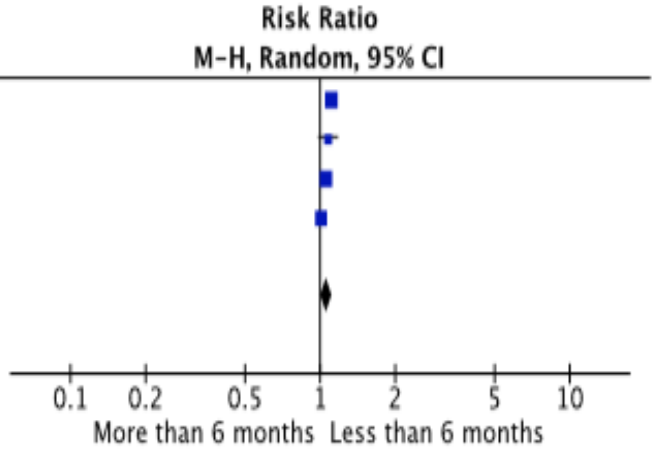
C Live birth

Study or Subgroup	Less than 6 months Events	Total	More than 6 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Love 2010	10856	12744	13977	18193	30.0%	1.11 [1.10, 1.12]
Wong 2015	349	445	169	232	13.6%	1.08 [0.98, 1.18]
DaVanzo 2012	3949	4596	4756	5839	29.3%	1.05 [1.04, 1.07]
DaVanzo 2007	1198	1366	1018	1171	27.0%	1.01 [0.98, 1.04]
Total (95% CI)		**19151**		**25435**	**100.0%**	**1.06 [1.01, 1.11]**
Total events	16352		19920			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 49.60$, df = 3 ($P < 0.00001$); $I^2 = 94\%$

Test for overall effect: Z = 2.53 (P = 0.01)



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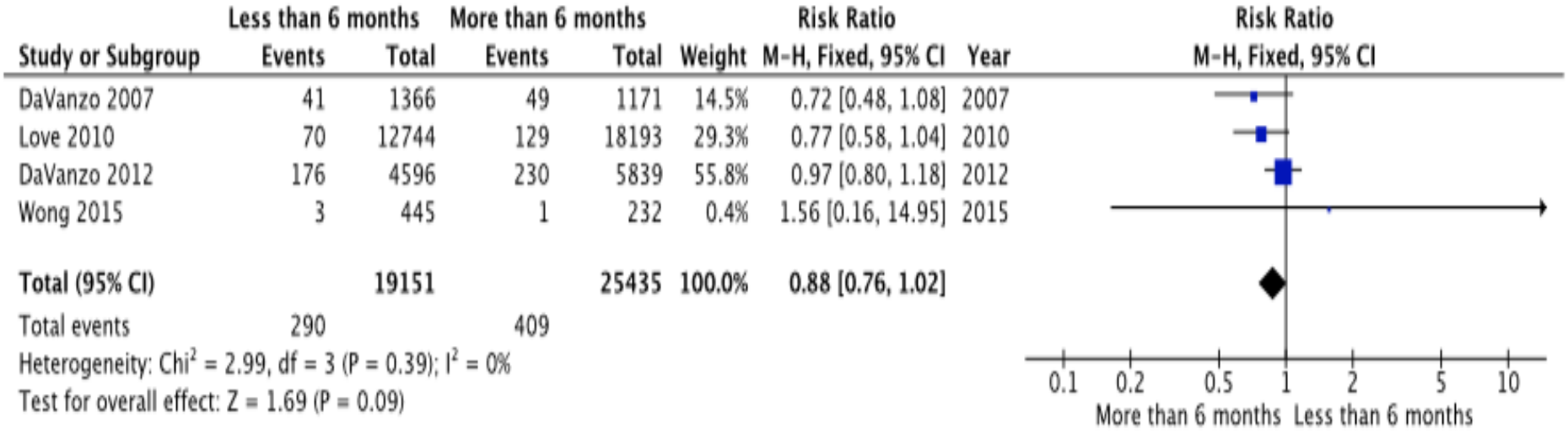
D. Stillbirth



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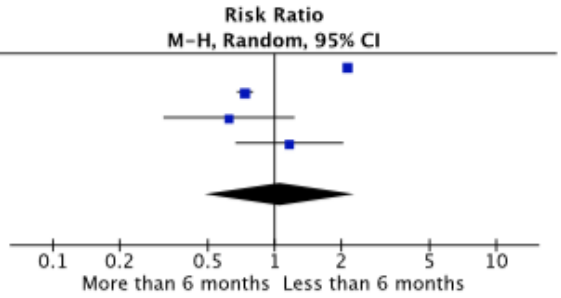
E Low birth weight

Study or Subgroup	Less than 6 months Events	Total	More than 6 months Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Conde- Agudelo 2004	2264	11615	22514	246493	27.0%	2.13 [2.05, 2.22]	2004
Love 2010	776	10856	1358	13977	26.9%	0.74 [0.68, 0.80]	2010
Bentolila 2013	10	92	26	149	22.4%	0.62 [0.32, 1.23]	2013
Makhlouf 2014	20	395	28	645	23.7%	1.17 [0.67, 2.04]	2014
Total (95% CI)		**22958**		**261264**	**100.0%**	**1.05 [0.48, 2.29]**	
Total events	3070		23926				

Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 539.34$, df = 3 ($P < 0.00001$); $I^2 = 99\%$

Test for overall effect: Z = 0.13 (P = 0.89)



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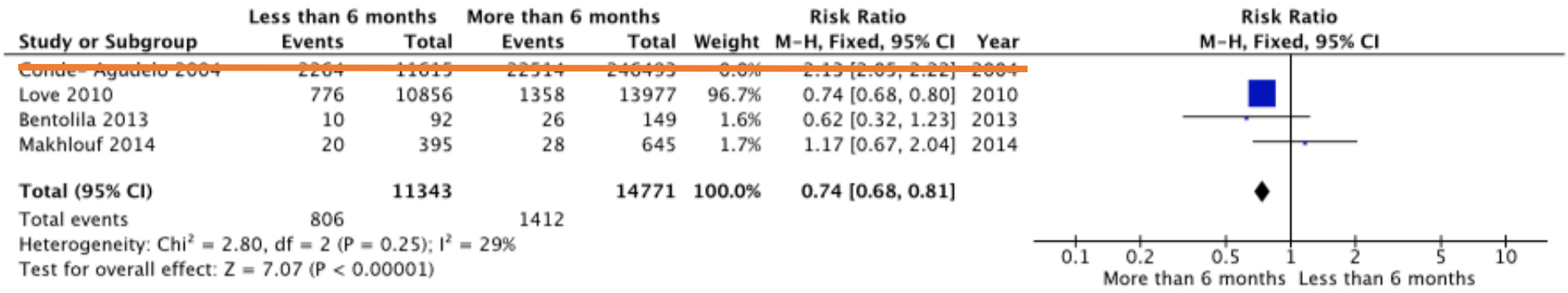

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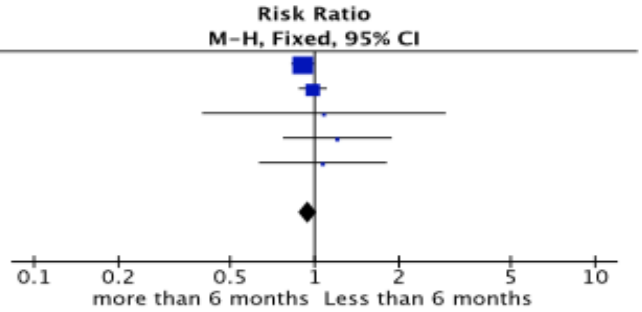
F. Pre –eclampsia

Study or Subgroup	Less than 6 months Events	Total	More than 6 months Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Conde- Agudelo 2004	421	11615	9839	246493	58.9%	0.91 [0.83, 1.00]	2004
Love 2010	485	10856	634	13977	36.9%	0.98 [0.88, 1.11]	2010
Bentolila 2013	6	92	9	149	0.5%	1.08 [0.40, 2.93]	2013
Makhlouf 2014	31	395	42	645	2.1%	1.21 [0.77, 1.88]	2014
Wong 2015	39	445	19	232	1.7%	1.07 [0.63, 1.81]	2015
Total (95% CI)		**23403**		**261496**	**100.0%**	**0.95 [0.88, 1.02]**	
Total events	982		10543				

Heterogeneity: $Chi^2 = 2.58$, df = 4 (P = 0.63); $I^2 = 0\%$

Test for overall effect: Z = 1.51 (P = 0.13)



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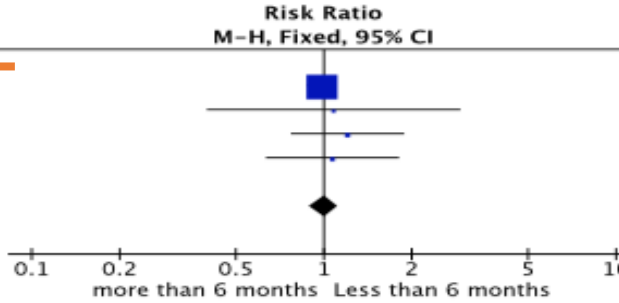
Study or Subgroup	Less than 6 months Events	Total	More than 6 months Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Love 2010	485	10856	634	13977	89.7%	0.98 [0.88, 1.11]	2010
Bentolila 2013	6	92	9	149	1.1%	1.08 [0.40, 2.93]	2013
Makhlouf 2014	31	395	42	645	5.2%	1.21 [0.77, 1.88]	2014
Wong 2015	39	445	19	232	4.0%	1.07 [0.63, 1.81]	2015
Total (95% CI)		**11788**		**15003**	**100.0%**	**1.00 [0.90, 1.12]**	
Total events	561		704				

Heterogeneity: $Chi^2 = 0.82$, $df = 3$ ($P = 0.84$); $I^2 = 0\%$

Test for overall effect: $Z = 0.01$ ($P = 0.99$)



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