PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

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<tr>
<th>TITLE (PROVISIONAL)</th>
<th>How Long After a Miscarriage Should Women Wait Before Becoming Pregnant Again? Multivariate Analysis of Cohort Data from Matlab, Bangladesh</th>
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<tr>
<td>AUTHORS</td>
<td>DaVanzo, Julie ; Hale, Lauren; Rahman, Mizanur</td>
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VERSION 1 - REVIEW

| REVIEWER            | Gold, Katherine  
|                     | University of Michigan, Department of Family Medicine |
| REVIEW RETURNED     | 04-Oct-2011 |

GENERAL COMMENTS

This paper addresses a very important topic about which there is limited data, particularly for low-income countries. Methods are well-described, and the size of the population used for study is impressive. The study has a potential to add vital information to this body of knowledge. In general, I think the study was reasonably done, and I am glad the authors are adding their findings to this literature.

My main concern is that while there is extensive discussion of how the current study compares to the similar study by Love the paper is very limited in considering how the results fit into the broader existing literature on this topic. Both the discussion and the limitations section are quite inadequate and result in a very narrow manuscript which does not adequately consider important issues.

My recommendation is that the manuscript in current form needs major revisions as detailed below.

Specific Comments
1. In the box: What is already known about this topic, I would dispute the assertion that the existing knowledge is “not known …for women in poor developing nations.” It is true that we don’t have a lot of knowledge, but there are other studies out there which have considered follow-up pregnancies after pregnancy loss, particularly stillbirth— the definition of those stillbirths (>20 wks) means that they would have counted as miscarriages in the current study.

2. Methods:
* first reference to “MCH-FP” needs to be spelled out.
* When you mention “for cases for which DLMP was not reported” please mention how many were in this group. It is not clear to me why you looked at EABs as an outcome.
* It seems to me that involuntary loss and voluntary termination have separate causes, implications, and outcomes, and it is odd to group them in a paper looking at IPI as a moderating factor.

3. Statistics:
* On p. 7, it is more accurate to simply state that the adjusted risk ratio for post-neonatal mortality for IPIs of 12-18 months is not significant rather than “nearly significant.”

4. Discussion: This section needs to be substantially expanded.
* Your results conflict with a number of prior studies showing higher risk of fetal death with short pregnancy interval. You definitely need to address this in the discussion. I was surprised how scant the reference list was and that many of the important studies appear to have been omitted. There is not a great deal of literature in this area to start with, but I would hope that the authors would do a careful reporting of what is out there since they have previously published in this area.
* Since Love only considered first pregnancies and you included all pregnancies, how is that likely to impact your results?
* I’m wondering if you can explain the seemingly conflictual findings that there is less fetal death and higher infant mortality with short IPI intervals. What might be the cause of that? Where does prematurity fit in to that?
* There is data from some studies which shows no higher rate of LBW with short IPIs suggesting that the “maternal nutrition depletion” may not be a valid hypothesis. What about the needs of other children draining maternal resources? * You cite the paper by Zhu as the source for the hypothesis of maternal depletion but that is not what their paper says…they say: some people have asserted this but it doesn’t explain our findings for poor outcomes with long intervals.
* Is this finding in your study because you included ALL pregnancies so moms would be more likely to have existing children at home? You need to think about and address all of these possibilities and expand your references of other similar studies.
* Not clear to me in methods or discussion why you included elective abortion in your outcomes since that has totally different mechanisms than a pregnancy loss or infant death. If you are going to include this, there needs to be some justification of it.
* There has been a great deal of discussion in the literature about the optimum spacing been around 18-23 months (give or take). I was surprised that this manuscript really did not address that prior finding and discuss how or whether the results here fit in with that previous recommendation.

5. Limitations: This section also needs significant expansion.
* The pregnancies are dated by LMP. There needs to be further discussion in the limitations section about how accurate this is. Also, can you reliably say that the prior loss was a miscarriage vs. stillbirth based on LMP dating of that pregnancy? Limitations should also address potential limitations from using average dating as you describe in the methods.
* I think a huge limitation of your study is that you did not measure LBW, prematurity, gestational age, so it is difficult to draw conclusions about your results. Not clear why that was not done
since I have seen that data in other studies of Matlab.

* I also think there needs to be a discussion about the definition of miscarriage and stillbirth. Some of the other studies out there define stillbirth starting at 20+ weeks, so their definition of stillbirth overlaps with your definition of miscarriage (before 28 weeks), meaning others have looked at some of these issues. Need to discuss how these different definitions might affect your results. * Similarly, re-
raises my question about how accurately you can define miscarriage based on LMP. Limitations should also acknowledge probable under-reporting of early miscarriages since these may not have been identified as pregnancies.

* Based on your comments about quality of prenatal care (p.9), I wonder whether women in Matlab are getting better care in the current pregnancy or in any pregnancy? Needs to be addressed in discussion or limitations.

* Why is the Conde-Agudelo study cited for their findings on long IPIs but not their findings on short IPIs (which appear to conflict with your findings?)

- The manuscript was reviewed by someone else but they did'nt give their permission.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer(s)' Comments to Author: Reviewer: 1 (Katherine J. Gold)

Comments:
This paper addresses a very important topic about which there is limited data, particularly for low-income countries. Methods are well-described, and the size of the population used for study is impressive. The study has a potential to add vital information to this body of knowledge. In general, I think the study was reasonably done, and I am glad the authors are adding their findings to this literature.

My main concern is that while there is extensive discussion of how the current study compares to the similar study by Love the paper is very limited in considering how the results fit into the broader existing literature on this topic. Both the discussion and the limitations section are quite inadequate and result in a very narrow manuscript which does not adequately consider important issues.

We have substantially expanded introduction and discussion section so that now the paper is set in the context of the larger literature on the effects of pregnancy spacing. We now reference many more studies than we did before.

My recommendation is that the manuscript in current form needs major revisions as detailed below.

Specific Comments
1. In the box: What is already known about this topic, I would dispute the assertion that the existing knowledge is “not known …for women in poor developing nations.” It is true that we don’t have a lot of knowledge, but there are other studies out there which have considered follow-up pregnancies after pregnancy loss, particularly stillbirth--the definition of those stillbirths (>20 wks) means that they would have counted as miscarriages in the current study.

The study that Dr. Gold recommended that looks at pregnancies following stillbirths (Black et al., 2007) compares their outcomes to outcomes of pregnancies following live births, but does not specifically look at the effects of the interval between the two pregnancies.

There are studies that consider intervals that began with a live birth or stillbirth (e.g., Conde-Agudelo et al., BMJ, 2000)), but these don’t distinguish between the two.
We now specifically mention that some of the pregnancies classified as miscarriages in our study may have been classified as stillbirths in studies using a 20-week cutoff.

2. Methods:
* first reference to “MCH-FP” needs to be spelled out.

Done.

* When you mention “for cases for which DLMP was not reported” please mention how many were in this group.

Done.

It is not clear to me why you looked at EABs as an outcome.

We looked at elective abortion because Love et al. considered “voluntary pregnancy termination,” and this allows for a direct comparison between the two studies.

* It seems to me that involuntary loss and voluntary termination have separate causes, implications, and outcomes, and it is odd to group them in a paper looking at IPI as a moderating factor.

We don’t group them. We treat (induced) abortion and miscarriage as separate categories.

3. Statistics:
* On p. 7, it is more accurate to simply state that the adjusted risk ratio for post-neonatal mortality for IPIs of 12-18 months is not significant rather than “nearly significant.”

We have revised the text to reflect this.

4. Discussion: This section needs to be substantially expanded.
* Your results conflict with a number of prior studies showing higher risk of fetal death with short pregnancy interval. You definitely need to address this in the discussion. I was surprised how scant the reference list was and that many of the important studies appear to have been omitted. There is not a great deal of literature in this area to start with, but I would hope that the authors would do a careful reporting of what is out there since they have previously published in this area.

We had focused on studies that assessed the effects of intervals that began with a miscarriage, and there are very few of those. We now mention other studies of the effects of interpregnancy intervals, including those that began with a live birth.

We have looked at all the studies that Dr. Gold very kindly suggested to us, but they all regard intervals that began (and ended) with a live birth or do not distinguish the type of outcome with which the interval began or do not look at the effect of IPI duration. We instead reference a meta-analysis and literature review that each summarize a number of studies of these issues.

* Since Love only considered first pregnancies and you included all pregnancies, how is that likely to impact your results?

We address this issue on page 9; we say “The Love et al. study only considers cases where the miscarriage that began the IPI was the first recorded pregnancy outcome for the woman, whereas we consider all IPIs that began with a miscarriage and control for gravidity in our
analyses. This may be one reason why we find greater effects of controlling for other
variables than they do. In our data there are only 2,461 first pregnancies that ended with a
miscarriage. We conducted our analysis for this sample and found patterns similar to those
reported here, but they were not statistically significant.”

* I’m wondering if you can explain the seemingly conflictual findings that there is less fetal
death and higher infant mortality with short IPI intervals. What might be the cause of that? Where
does prematurity fit in to that?

Unfortunately we do not have data on prematurity for a large enough sample of IPIs that
began with a miscarriage to investigate this directly. We say on pages 9-10 that “Our results
for infant mortality (but not for pregnancy outcomes) are consistent with the idea that
pregnancies that result in miscarriages nutritionally deplete vital nutrients and that women
require time to replete them in order to give birth to a healthy child that will survive its first
year. Our finding of a pernicious effect for children but not for women is consistent with
studies that show that the effects of maternal depletion can be different for the mother and the
fetus, with the fetus being affected more than the mother in cases of severe nutritional
deficiencies.”

* There is data from some studies which shows no higher rate of LBW with short IPIs
suggesting that the “maternal nutrition depletion” may not be a valid hypothesis.

It is true that some studies have not found significantly higher LBW for short IPIs, but the
majority of the studies reviewed by Condo-Agudelo et al. (JAMA 2006) find significantly higher
rates of LBW for short IPIs following live births.

What about the needs of other children draining maternal resources?

This is possible, but we view it as beyond the scope of our paper. We do control for gravidity
in our multivariate analysis. (We recognize that this is not the same as the number of living
children, but the two are likely to be correlated.)

* You cite the paper by Zhu as the source for the hypothesis of maternal depletion but that is
not what their paper says…they say: some people have asserted this but it doesn’t explain our
findings for poor outcomes with long intervals.

Zhu et al. (1999) say “The relation between short interpregnancy intervals and adverse
perinatal outcomes has been attributed to maternal nutritional depletion and postpartum
stress” (p. 593) and cite Miller and Winkvist et al. for this statement. Zhu et al. go on to say
“However, it is unknown why a long interpregnancy interval is associated with adverse
perinatal outcomes” (p. 593) and then offer two hypotheses for the effects of long intervals.
Our citation for Zhu et al. is not for a statement about maternal depletion but is for the
statement “It has also been hypothesized that one pregnancy prepares the woman’s body for
the next and that this ‘protection’ decreases as time passes, making pregnancies following
long intervals similar to first pregnancies, which have been shown to have higher risk of many
poor outcomes.” We have added a citation to Winkvist regarding maternal depletion.
* Is this finding in your study because you included ALL pregnancies so moms would be more likely to have existing children at home? You need to think about and address all of these possibilities and expand your references of other similar studies.

It is true that some of the women will have other children at home, but this is not directly related to the IPI variable we consider, which measures the duration of the interval between a preceding miscarriage and the conception of the focal pregnancy. Since the pregnancy that began the interval was a miscarriage, it did not result in the birth of an “existing child at home.” As noted above, we do control for gravidity in our multivariate analysis.

* Not clear to me in methods or discussion why you included elective abortion in your outcomes since that has totally different mechanisms than a pregnancy loss or infant death. If you are going to include this, there needs to be some justification of it.

As noted above, we look at elective abortions because Love et al. considered “voluntary pregnancy termination.”

* There has been a great deal of discussion in the literature about the optimum spacing been around 18-23 months (give or take). I was surprised that this manuscript really did not address that prior finding and discuss how or whether the results here fit in with that previous recommendation.

The literature varies greatly in what it recommends about “optimum spacing,” depending on what type of outcome is considered (maternal, perinatal, infant, child, under-five; mortality or other indicators of health) and how intervals are defined (particularly whether the study distinguishes the type of pregnancy outcome with which the interval began).

Zhu et al. (1999) find the lowest risks of adverse perinatal outcomes for IPIs of 18-23 months duration. That study only considers intervals that began with live births.

Conde-Agudelo’s meta-analysis of the effects of intervals following live births on perinatal outcomes (JAMA 2006) found that intervals of 18-59 months are associated with better outcomes than shorter and longer intervals, and his review of studies of maternal outcomes (AJOG 2007) had a similar conclusion.

Rutstein (2008 DHS working paper) found infant mortality to be lowest for intervals that began with live births of at least 24 months and under-five mortality to be lowest for intervals of at least 36 months.

At its technical consultation in June 2005, WHO made two recommendations regarding pregnancy spacing:

“After a live birth, the recommended interval before attempting the next pregnancy is at least 24 months in order to reduce the risk of adverse maternal, perinatal and infant outcomes.”
“After a miscarriage or induced abortion, the recommended minimum interval to next pregnancy should be at least six months in order to reduce risks of adverse maternal and perinatal outcomes.”

However, the latter recommendation was based on one study (Conde-Agudelo et al., IJGO 2005) of Latin America of the effects of intervals following induced and spontaneous abortions. The study was not able to distinguish between the two types of abortion. However, there are reasons to expect that the effects might differ considerably for the two types – one being a voluntary termination of a pregnancy that was most likely unintended, and the other being the unexpected termination of a pregnancy that was most likely intended. In fact, the report on the WHO Technical Consultation recommended “More studies on the effects of post-abortion pregnancy intervals are needed in different regions. A distinction between induced and spontaneous abortion … would be particularly helpful in future studies” (p. 3). Our study, like that of Love et al. for Scotland and several other studies that we now mention, has looked specifically at the effects of intervals following miscarriages (spontaneous abortions).

These issues are now all discussed in the paper.

I would like to note that WHO is currently conducting their own evidence review of pregnancy spacing outcomes, and the results should be available soon.

5. Limitations: This section also needs significant expansion.

We have expanded the Discussion section to mention all of the issues raised herein.

* The pregnancies are dated by LMP. There needs to be further discussion in the limitations section about how accurate this is.

The reporting of DLMP is likely to be quite accurate in the Matlab DSS because the data were collected frequently, with relatively short recall periods. Sonography is rare in Matlab (it has been done only for a few special studies), so we do not have the option of using information from that to calculate pregnancy gestation. We now mention these issues in the paper.

Also, can you reliably say that the prior loss was a miscarriage vs. stillbirth based on LMP dating of that pregnancy? Limitations should also address potential limitations from using average dating as you describe in the methods.

We now specifically discuss the fact that the DSS defines a stillbirth as a fetal loss at 28 weeks or longer gestation and defines spontaneous abortion, or miscarriage, as a spontaneous fetal loss prior to 28 weeks and that some studies define stillbirth starting at 20+ weeks, so their definition of stillbirth overlaps with our definition of miscarriage. We have examined the extent of this by looking at the frequency distribution of pregnancy duration by type of outcome for cases for which we know DLMP. There were 50 (of 578 cases) where the outcome of the focal pregnancy was coded as miscarriage that had a duration of gestation of 20-27 weeks. We are not able to recode these cases because we don’t know pregnancy
duration for cases for which DLMP is not reported and must rely on the reported pregnancy outcome for those cases. The fact that we find no evidence of maternal depletion on pregnancy outcomes even with a miscarriage definition of 28+ weeks suggests that we would not have seen one had we been able to use a 20+-week definition.

Also see response to the comment above this one.

* I think a huge limitation of your study is that you did not measure LBW, prematurity, gestational age, so it is difficult to draw conclusions about your results. Not clear why that was not done since I have seen that data in other studies of Matlab.

We would have loved to analyze data on LBW, prematurity, and gestational age, but such information is only available for a small subset of all pregnancies in the DSS. Since we restrict our attention to the subset of pregnancies in the DSS that were preceded by a miscarriage, we would not have enough cases with information on LBW, prematurity, and gestational age for our analysis. Most likely the studies the reviewer saw did not restrict their samples to live births that were immediately preceded by a miscarriage.

Also see responses to the comments above this one.

* I also think there needs to be a discussion about the definition of miscarriage and stillbirth. Some of the other studies out there define stillbirth starting at 20+ weeks, so their definition of stillbirth overlaps with your definition of miscarriage (before 28 weeks), meaning others have looked at some of these issues. Need to discuss how these different definitions might affect your results. *

Similarly, re-raises my question about how accurately you can define miscarriage based on LMP.

As noted above, for cases for which we know DLMP, we have looked at the frequency distribution of pregnancy duration by type of outcome of the focal pregnancy. There were 50 (of 578 cases) coded as miscarriage that had a duration of gestation of 20-27 weeks. We now note this in the Strengths and weaknesses section of paper. It appears that Love et al use a definition of gestation < 24 months for miscarriages (“Miscarriage or spontaneous pregnancy loss before 24 completed weeks on gestation ….” (p. 1).

Also see comments about this issue.

Limitations should also acknowledge probable under-reporting of early miscarriages since these may not have been identified as pregnancies.

Done.

* Based on your comments about quality of prenatal care (p.9), I wonder whether women in Matlab are getting better care in the current pregnancy or in any pregnancy? Needs to be addressed in discussion or limitations.

Better care in compared to what/ when -- the Comparison Area? Scotland? earlier years? We say on p. 4 “The MCH-FP Area has … greater coverage of antenatal care and better access to basic and emergency obstetric care than the Comparison Area.” We do control for whether the woman lived the MCH-FP Area or Comparison Area in our multivariate analysis. Near the end of the paper (on p. 11) we say “We do not consider some possibly confounding variables, e.g., use and quality of prenatal care and the woman’s health and fecundity, that may affect the outcomes of interest and could illuminate the mechanisms underlying the effects that we find.”
* Why is the Conde-Agudelo study cited for their findings on long IPIs but not their findings on short IPIs (which appear to conflict with your findings?)

We now cite several Conde-Agudelo et al. studies and mention their relevant findings regarding both short and long intervals.

VERSION 2 – REVIEW

| REVIEWER               | Gold, Katherine  
The University of Michigan, Department of Family Medicine |
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<td>REVIEW RETURNED</td>
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GENERAL COMMENTS

Thank you for allowing me to review this revised manuscript. I very much appreciate the efforts of the authors to address my comments and found the revision much easier to understand. I may have misunderstood their unique focus on IPI after miscarriage but this angle became much more clear in the revised draft. I also appreciated the much-expanded discussion section which I think highlights important issues in the literature. I think the authors have made excellent improvements to the manuscript and appreciate their thoughtful revisions. I would recommend publication.

| REVIEWER               | Lucke, Jayne  
The University of Queensland, UQ Centre for Clinical Research |
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<td>REVIEW RETURNED</td>
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GENERAL COMMENTS

I recommend that this paper be published.

It presents an important finding and makes a significant contribution to the emerging literature about pregnancy outcomes following reproductive events. It demonstrates the importance of maintaining large longitudinal cohorts for ongoing analysis in both developed and developing countries. The paper is well written, the data is comprehensively analysed and reported, and the implications for further research and clinical practice are well presented. The suggestions of previous reviewers have been considered carefully, addressed thoroughly and incorporated into the revision appropriately.

Minor comments:

Page 29, line 32: Given what we know about the high rate of unintended pregnancies (that may or may not subsequently become wanted pregnancies/children) it is not necessarily correct to assume
that unexpected terminations are most likely intended pregnancies.  

Page 27, line 36: "a" should be "as"; i.e. "how mortality varies with duration of IPI are not as smooth..."

Jayne Lucke  
UQ Centre for Clinical Research, The University of Queensland