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How Long After a Miscarriage Should Women Wait Before Becoming Pregnant Again? Multivariate Analysis of Cohort Data from Matlab, Bangladesh

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ABSTRACT

Objective To determine the optimum interpregnancy interval (IPI) following a miscarriage.

Design Multivariate analysis of population-based, prospective data from a demographic surveillance system.

Setting Pregnancies in Matlab, Bangladesh, between 1977 and 2008.

Participants 9,214 women with 10,453 pregnancies that ended in a miscarriage and were followed by another pregnancy outcome.

Main outcome measures Outcome of pregnancy following the miscarriage was singleton live birth, stillbirth, miscarriage, or induced abortion. For pregnancies that ended in live birth: early neonatal, late neonatal, and post-neonatal mortality.

Results Compared with interpregnancy intervals (IPIs) of 6-12 months, pregnancies that were conceived ≤3 months after a miscarriage were more likely to result in a live birth and less likely to result in a miscarriage (adjusted odds ratio 0.70, 95% confidence interval 0.57 to 0.86) or induced abortion (0.50, 0.29 to 0.89). Induced abortions were significantly more likely following IPIs of 18-24 months (2.36, 1.48 to 3.76), 36-48 months (2.73, 1.50 to 4.94), and >48 months (3.32, 1.68 to 2.95), and miscarriages were more likely following IPIs of 12-17 months (1.25, 1.01 to 1.56) and >48 months (1.90, 1.40 to 2.58). No significant effects of IPI duration are seen on the risks of a stillbirth. However, IPIs ≤3 months following a miscarriage are associated with significantly higher late neonatal mortality for the infant born at the end of the IPI (adjusted relative risk ratio 1.74, 1.06 to 2.84), and IPIs of 12-18 months are associated with a significantly lower unadjusted risk of post-neonatal mortality (0.54, 0.30 to 0.96).

Conclusions The shorter the IPI following a miscarriage, the more likely the subsequent pregnancy is to result in a live birth. However, very short IPIs may not be advisable in poor countries like Bangladesh because they are associated with a higher risk of mortality for the infants born after them.

ARTICLE SUMMARY

Article Focus

- To assess the association between the duration of the interpregnancy interval (IPI) following a miscarriage and the outcome of the next pregnancy in Matlab, Bangladesh

Key Messages

- The shorter the IPI following a miscarriage, the more likely the subsequent pregnancy is to result in a live birth.
- However, very short IPIs (≤3 months) are associated with a higher risk of late neonatal mortality for the infants born after them.
- Hence, IPIs ≤3 months may not be advisable in poor countries like Bangladesh.

Strengths and Limitations of this Study

- Study considers data from a poor developing area – rural Bangladesh. Most previous studies of this topic have been of industrialized countries.
- Sample size (10,453) is larger than that in most studies of this topic, though not as large as in a recent study of Scottish women.
- Study considers mortality during infancy in addition to pregnancy outcomes.
- Study considers effects of even shorter and even longer intervals than previously considered.
- Data on pregnancy outcomes were carefully collected and likely to be of high quality, but probably not as high quality as clinical data.

INTRODUCTION

Many studies have assessed the effect on maternal[1] and perinatal[2] outcomes and on infant and child mortality[3] of pregnancy spacing following a live birth or following a live birth or stillbirth. However, very few studies have sought to identify the optimum interpregnancy interval (IPI) following a miscarriage (spontaneous abortion); the studies that have been done are generally of women living in industrialized countries, and most have relatively small sample sizes.[4 5 6] A recent study[7] that considered a large sample of women who delivered in Scottish hospitals found that women who conceived within six months after a miscarriage had better outcomes of the subsequent pregnancy than women who waited longer to conceive again; e.g., they were less likely to have a voluntary pregnancy termination (induced abortion) or another miscarriage. In this paper we investigate whether these same findings are seen in a very different setting – among poor women in rural Bangladesh. We also investigate whether infants born at the ends of the intervals died before their first birthday. Women in Bangladesh are more likely to be malnourished than those in industrialized countries,[8] and hence may be more likely to be nutritionally depleted by a pregnancy, even one that ends in miscarriage.

METHODS

We use high-quality longitudinal data from the Matlab Demographic Surveillance System (DSS). Matlab is a rural sub-district of Bangladesh that is well known for its DSS and its Maternal Child Heath-Family Planning (MCH-FP) project, which operates in half of the area covered by the DSS to provide intensive and quality family planning and maternal/child health services.[9 10 11]

The Matlab DSS contains, for both areas of Matlab, longitudinal records of pregnancy outcomes and deaths for all household members. During their regular visits to each household, fortnightly between 1966 and 1999, monthly between 2000 and 2006, and bimonthly since 2007, the community health workers (CHWs) record pregnancy status at the time of the visit and any pregnancy outcomes or household deaths that occurred prior to the visit.

The DSS provides information on 245,091 pregnancies that occurred between 1974 and 2008. In this study we consider the 10,435 pregnancies documented in the DSS that began with a miscarriage in January 1977 or later and were followed by another pregnancy outcome (here called the "focal pregnancy") other than a multiple live birth not later than December 2008. Before 1977, the DSS did not distinguish between spontaneous and induced abortions. In the DSS, a miscarriage (spontaneous abortion) is defined as a spontaneous fetal loss prior to 28 weeks gestation. We exclude from the sample focal pregnancies that ended with multiple live births; 246 pregnancies are excluded for this reason.

We consider the following outcomes of the focal pregnancies that follow the IPI after a miscarriage: singleton live birth, stillbirth, miscarriage, and induced abortion. In the DSS, a *live birth* is the delivery of a live baby at any gestational age; a *stillbirth* is a fetal loss at 28 weeks or longer gestation; and *induced abortion* is self-reported. Early-gestation pregnancy termination is legal in Bangladesh if performed in a medical setting before the pregnancy is clinically confirmed. Such pregnancy terminations are done by manual vacuum aspiration by trained female paramedics at the government Health and Family Welfare Centers and are known as "menstrual regulation" (MR). MR can be performed within 8 weeks of the last menstrual period before pregnancy is clinically confirmed. MR has been available through government and other medical facilities in Bangladesh since the late 1970s, when the government agreed to permit such pregnancy terminations in an effort to replace the practice of unsafe abortion. Pregnancy termination in a non-medical setting or after pregnancy is clinically confirmed is prohibited in Bangladesh except when done to save a woman's life. Our "induced abortion" category includes both MRs and voluntary pregnancy terminations by other means. (Since 1989, when method of pregnancy termination was first distinguished in the DSS, 52% of terminations have been by MR, 3% by D&C, and 45% by other means.)

We also consider mortality of the children born in the focal pregnancies during three subperiods of the first year of life – early neonatal (first week of life), late neonatal (next three weeks of life), and post-neonatal (the rest of the first year of life). The sample for our analyses of early neonatal mortality is the 8,705 IPIs that began with a miscarriage and ended with a live birth. The sample for late neonatal mortality is the 8,401 of these that survived the first week of life and were still living in Matlab, and the sample for post-neonatal mortality is the 8,268 of these that survived the first four weeks of life and were still living in Matlab.

The duration of the IPI is defined by measuring the amount of time between the preceding miscarriage and the estimated date of conception of the focal pregnancy. For the 5,914 cases for which we know the date of the last menstrual period (DLMP), we estimate the date of conception as occurring two weeks after the DLMP before the focal pregnancy. For the 4,519 cases for which DLMP was not reported, we estimate the duration of the IPI as the amount of time between the miscarriage and the end of the focal pregnancy less the estimated duration of the focal pregnancy, based on the outcome of that focal pregnancy. Our estimate of duration of each type of pregnancy outcome is the average duration of all pregnancies that ended with that outcome for which we know DLMP. These averages are 36 weeks for live births, 33 weeks for stillbirths, 11 weeks for miscarriages, and 8 weeks for induced abortions. We have also done all analyses only for the cases for which DLMP was reported; the sizes of the odds ratios and relative risks are similar to those reported here.

Our multivariate analyses control for the woman's age at the time of the focal outcome (with dichotomous indicators for age <20, 20-24, 25-29, 30-34, 35-39, and ≥40), the woman's educational attainment, and calendar year (approximately 10-year bands of the calendar year of the focal outcome). (We used interactions to explore whether the IPI effects varied over time, but these were never statistically significant.) We also control for the gravidity of the focal pregnancy (dichotomous indicators) and for whether the woman lived in the MCH-FP Area or the Comparison Area of Matlab. Data on maternal age, gravidity, area, and calendar year all come from the DSS. Information on women's education is from periodic censuses conducted by icddr,b in the Matlab area. Most of the potential confounders vary significantly with IPI, as can be seen in Table 1. Women's ages at both the beginnings and ends of the IPI are positively related to IPI duration, and longer IPIs are more likely to be for higher gravidity and to occur in the later years covered by the data.

Statistical analysis

We assess the effects of the duration of the IPI on the outcome of the subsequent pregnancy with unadjusted and adjusted odds ratios that derive from univariate and multivariate multinomial logistic regressions. The effects of IPI duration on mortality during subperiods of infancy are estimated with Cox proportional hazards models. All models are estimated by Stata 11.0. The hazard model allows for censoring due to moving out of the Matlab area or not completing the at-risk period by the end of 2008. The multivariate analyses control for the variables mentioned above. We used the cluster command in Stata 11.0 to adjust standard errors for the fact that 1,516 women have more than one pregnancy in the sample.

To facilitate comparisons we consider the same categories of IPI durations considered in the recent Love et al. study of Scottish women -- ≤6 months (0 to 24 weeks), 6-12, months (25-52 weeks) (reference category), 12-18 months (53 -76 weeks), 18-24 months (77-104 weeks), and >24 months (105 or more weeks), where each category includes the upper bound but not the lower bound. We also conduct analyses that consider additional categories of IPIs, breaking the ≤6 months category into ≤3 months (0-12 weeks) and 4-6 months (13 -24 weeks) to assess the effects of very short intervals, and breaking the >24 months category into 24-36 months, 36-48 months, and >48 months, since other studies have found different effects of such longer intervals.[12]

RESULTS

The middle of Table 2 shows the cross-tabulation of IPI duration and outcome of the focal pregnancy for the IPI categories considered by Love et al. The rows above that show the finer breakdown of the ≤6 months category, and the rows below that show the finer breakdown of the >24 months category. Of the 10,435 cases in our sample, 4,596 (44.0%) conceived ≤6 months after the miscarriage (20.5% ≤3 months and 23.5% in 4-6 months). The next largest percentage is for IPIs of 6-12 months (28.0%). The percentages for IPIs of 12-18 and 18-24 months are 9.5% and 6.5%, respectively. IPIs >24 months comprise 12.0% of the sample (5.5% are 24-36 months long, 2.8% are 36-48 months, and 3.7% are >48 months). We find a somewhat higher incidence of short intervals (≤12 months) and a somewhat lower incidence of long intervals (>24 months) than Love et al. find for Scottish women, but, as seen in the right-hand column of Table 2, the IPI distributions are quite similar.

Of all IPIs that began with a miscarriage, 2.1% ended with an induced abortion, 10.6% ended with another miscarriage, 3.9% ended with a stillbirth, and 83.4% ended with a live birth (Table 2). The percentage of post-miscarriage pregnancies that end with a live birth decreases as the length of the IPI increases. It is highest for the shortest IPIs (85.9% for IPI ≤6 months and 87.7% for IPI ≤3 months) and lowest for the longest IPIs (77.1% for IPI >24 months and 71.1% for IPI >48 months). The percentages for induced abortion and miscarriage each increase nearly monotonically as IPI increases, but there is little systematic pattern for stillbirths. A similar pattern was found for Scottish women, as can be seen in Table 2, though the incidence of stillbirth is lower in their data and the incidence of induced abortion higher than we find for Matlab, Bangladesh.

Of all IPIs that began with a miscarriage and ended with a live birth, 292 of those live-born children died in their first week of life (33.5 early neonatal deaths per 1,000 live births). Of those who survived the first week, 13.1/1,000 died in the next three weeks. And of those who survived the first four weeks, 26.6/1,000 died before their first birthday (Table 3). The patterns of how mortality varies with duration of IPI are not as smooth as those for pregnancy outcomes, but they show that the risks of mortality are often higher for the shorter IPIs and lower for the longer IPIs. The percentage of babies known to be alive at one year is below the sample average for IPI ≤3 months and above the sample average for 3 months < IPI ≤36 months.

The patterns of how the unadjusted and adjusted odds ratios of the outcome of the focal pregnancy vary with IPI duration are quite similar in our data and in the Love et al. data on Scottish women (Figure 1). In both studies, no significant effects of IPI duration are seen on the risks of a stillbirth, but the unadjusted odds of induced abortion increase monotonically as IPI duration increases, being lowest for IPI ≤6 months (for Matlab unadjusted OR for IPI ≤6 months = 0.59, 95% confidence interval 0.40 to 0.86, relative to IPI=6-12 months) and highest for IPIs>24 months (for Matlab unadjusted OR= 3.07 [2.11 to 4.46] relative to IPI=6-12 months). In Matlab, the unadjusted odds of a subsequent miscarriage also generally increase with IPI duration, being highest for IPIs >24 months, whereas in Scotland long IPIs were not associated with higher odds of miscarriage. For both induced abortion and miscarriage, the patterns are very similar in the two studies for the shortest IPIs, but the pernicious effects of long intervals on the unadjusted odds are larger for Matlab than in Scotland. Adjusting for other variables generally has more effect in our data from Matlab than it did in the Scottish data. In the Matlab data, the effect of adjustment is greatest for the longest intervals, so much so that the adjusted OR for IPIs>24 months on induced abortion is slightly lower for Matlab than for Scotland.

Unadjusted and adjusted odds ratios of the focal-pregnancy outcome for our finer breakdown of IPI categories show that the same patterns persist *within* the IPI≤6 months and IPI>24 months categories (Figure 2), though the odds of a live birth for 24-36 months are lower than those for 18-24 months. Relative to IPI=6-12 months, pregnancies that were conceived ≤3 months after a miscarriage were the most likely to result in a live birth and least likely to result in a miscarriage (adjusted odds ratio 0.70, 95% confidence interval 0.59 to 0.86) or induced abortion

(0.50, 0.29 to 0.89). Induced abortions were more likely following IPIs of 18-24 months (2.36, 1.48 to 3.75), 36-48 months (2.73, 1.50 to 4.94), >48 months (3.32, 2.05 to 5.38); and miscarriages were more likely following IPIs of 12-17 months (1.25, 1.01 to 1.56) and >48 months (1.90, 1.40 to 2.58). Again, adjustment has a greater effect the longer the IPI. Again, no significant effects of IPI duration are seen on the risks of a stillbirth.

Figure 3 shows the hazard ratios of mortality during the three subperiods of infancy for our finer breakdown of IPI categories. We find no significant relationships between IPI duration and early neonatal mortality in our unadjusted or adjusted analyses. However, for late neonatal mortality, in both the unadjusted and the adjusted analyses, we find significantly higher risk of mortality for IPIs ≤3 months (adjusted relative risk ratio 1.74, 1.06 to 2.84) and generally see a decline in mortality as IPI duration increases up to 36 months. We find a significantly lower unadjusted risk of post-neonatal mortality for IPIs of 12-18 months compared to those of 6-12 months (0.54, 0.30 to 0.96). (The adjusted risk ratio is similar but is not statistically significant [0.56, 0.31 to 1.01].)

DISCUSSION

We find that the shorter IPI following a miscarriage, the more likely the subsequent pregnancy is to result in a live birth. Women with IPI>18 months following a miscarriage, and especially those with IPI>48 months have a much higher likelihood of experiencing another miscarriage or having an induced abortion. The odds of an induced abortion following a miscarriage are particularly high for the longest IPI category (unadjusted OR for IPI>48 months = 5.02 [3.13 to 8.03] and adjusted OR = 3.32 [2.05 to 5.38]). Adjusting for the effects of demographic and socioeconomic variables reduces the effect of long intervals on induced abortion, but they remain large and significant. No significant effects of IPI duration are seen on the risks of a stillbirth.

However, we see quite different patterns when we consider the effect of pregnancy spacing after a miscarriage on late neonatal and post-neonatal mortality. Compared to IPIs of 6-12 months, the shortest IPIs following a miscarriage (≤3 months) are associated with significantly higher unadjusted and adjusted risks of late neonatal mortality, and IPIs of 12-18 months are associated with a significantly lower unadjusted risk of post-neonatal mortality. It appears that children born after very short IPIs following a miscarriage are able to survive the first week of life but then are at higher risk of dying in the rest of the first year.

Comparison to other studies

Most studies of the effects of pregnancy spacing consider intervals that began with a live birth or with a live birth or stillbirth.[1-3 13] They generally find adverse effects of both short and long intervals, but the "optimum" interval (the one with the lowest risk of an adverse outcome) differs across types of outcomes. For example, a study of the U.S. that considers intervals that began with live births finds the lowest risks of adverse perinatal outcomes for IPIs of 18-23 months duration.[14] A meta-analysis of the effects of intervals following live births on perinatal outcomes found that intervals of 18-59 months are associated with better outcomes than shorter and longer intervals,[2] and a review of studies of maternal outcomes reaches a similar conclusion.[1] An analysis of data from a number of developing countries found infant mortality to be lowest for intervals >24 months duration that began with live births, and under-five mortality to be lowest for intervals >36 months.[3]

A study of the Matlab MCH-FP Area found that following live births the risks of miscarriage and of stillbirth in the next pregnancy were significantly higher for IPIs ≤6 months (compared to those of 27-50 months duration).[12] That study did not distinguish the type of outcome that began IPIs >50 months. An earlier study in Bangladesh found a higher risk of early fetal death (first or second trimester) following short IPIs (<12 months) that began with the birth of a surviving child who breastfed.[15] Studies using data from Sweden found that very short (≤3 months) IPIs following live births were associated with higher risks of stillbirth.[16 17] Studies of

World Fertility Survey data from a number of developing countries found IPIs <9 months following live births to be associated with higher risks of fetal death;[18 19] early fetal losses and stillbirths were combined in those studies.

Very few studies have looked specifically at IPIs that began with a miscarriage, as we do here. A study of Latin America that assessed the effects of intervals following induced and spontaneous abortions found that intervals <6 months between abortion and subsequent pregnancy were associated with elevated risks of premature rupturing of membranes, anemia and bleeding, pre-term and very pre-term births, and low birthweight, compared with longer intervals.[20] However, that study did not distinguish between induced and spontaneous abortions. There are reasons to expect that the effects might differ considerably for the two – 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 more likely to have been intended. Based on the study of Latin America just mentioned, WHO currently recommends "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."[21] The report on the WHO Technical Consultation that makes that recommendation comments "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).[21]

Three studies[4-6] using data from the U.S. or Europe find no effects of the duration of IPI following a miscarriage on the outcome of the subsequent pregnancy, but their samples are relatively small (64, 91, and 1,530 respectively). An earlier study of Matlab that considered a much smaller sample of IPIs that began with a miscarriage than that considered here and only in the MCH-FP Area also found, as we do here, a decreasing likelihood of having a live birth following a miscarriage as duration of the preceding IPI increases.[12] However, that study did not consider longer intervals that began with a miscarriage.

Love et al.'s recent study uses a large sample of pregnancies to Scottish women who had a miscarriage to assess the effects of pregnancy spacing on the outcome of the subsequent pregnancy.[7] We have constructed our analyses to be as similar as possible to those of Love et al., to facilitate comparisons. Our results for pregnancy outcomes are remarkably similar to theirs. Both studies find that short IPIs following a miscarriage are associated with lower risks of a subsequent miscarriage or an induced abortion, and long intervals are associated with higher risks of these outcomes, and both find no significant effects of the duration of the post-miscarriage IPI on the risk of stillbirth.

We also examine even shorter and longer IPIs durations than Love et al. do and show that the very shortest intervals we consider (≤3 months) are associated with the lowest risks of induced abortion and miscarriage and the longest (>48 months) are associated with the highest risks of these outcomes.

We generally find even stronger pernicious effects of long intervals on the odds of a miscarriage or an induced abortion in the focal pregnancy than was found for Scottish women, and the effects are particularly large when we consider an expanded set of IPI categories (up to >48 months). Adjusting for the effects of demographic and socioeconomic variables reduces the effects of long intervals on the likelihood of induced abortion more for Matlab than it did in Love et al.'s study of Scotland; the adjusted risk associated with IPI >24 months (compared to those of 6-12 months) is slightly lower for Matlab than those Love et al. found for Scotland (whereas the opposite is true for unadjusted risks). 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 2,461 first pregnancies that ended with a miscarriage. We conducted our

analysis for this subsample and found patterns similar to those reported here, but they were not statistically significant.

We find some evidence that short IPIs following miscarriages are associated with higher mortality between the first week and the end of the first year of life for the children born after a miscarriage. Another study of Matlab found that short inter-outcome intervals (<15 months between one pregnancy outcome and the next outcome) that began with a miscarriage were associated with higher risks of early and late neonatal mortality compared with intervals of 36-59 months that began with the live birth of a child who survived.[22] (However, that study did not compare them to longer intervals that began with a miscarriage.) By contrast Love et al. do not find short IPIs to be associated with higher risks of preterm delivery and low birthweight – outcomes that have been widely found to be associated with mortality during infancy.[23 24] The better nutritional status of Scottish women may buffer their fetuses from the depleting effects of a recent previous miscarriage.

Previous studies have offered a number of hypotheses to explain why there might be adverse effects of short IPIs, the main ones being (1) competition for family resources and time from a just-older sibling;[22] (2) transmission of infection among closely-spaced siblings;[22] and (3) maternal depletion,[25] especially of folate.[26] The first and second mechanisms would only come into play for intervals that began with live births of children who survived, and hence do not apply to IPIs that began with miscarriages. Maternal depletion is more likely the longer the pregnancy.[33] Folate depletion begins around 5 months gestation.[34] Since our definition of miscarriages includes pregnancies up to 28 weeks gestation, some of the pregnancies could lead to folate depletion. 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.[27]

Our finding that short IPIs following a miscarriage are associated with a greater likelihood of a live birth at the end of the interval is consistent with the notion that most women who had a miscarriage wanted to have a live birth, and as a result many of them seek to become pregnant again as soon as possible and may take very good care of themselves during the subsequent pregnancy. A fifth (20.5%) of the women in our sample who experienced a miscarriage and became pregnant again did so within three months of the miscarriage, and 44.0% were pregnant within six months.

To explain the adverse effects of long IPIs on pregnancy outcomes, it has 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,[14] which have been shown to have higher risk of many poor outcomes.[28] It is also possible that long intervals are selective of women in poorer health, who take longer to conceive,[29] or that women who have long intervals did not want to become pregnant again and do not take as good care of themselves during pregnancy.[12] In addition, long IPIs are more likely for older women; older maternal age is associated with its own independent adverse effects on pregnancy outcomes,[30] though we see an effect even when we control for maternal age. A meta-analysis has shown that IPIs longer than 59 months are associated with adverse perinatal outcomes.[2] That study also found adverse effects on perinatal outcomes of intervals shorter than 18 months, which we do not see for pregnancy outcomes, but we do see some adverse effects of very short intervals on infant survival. Other studies of Matlab have shown that women with long intervals (but not distinguishing the type of outcome with which they began) have higher risks of pregnancy complications,[31] maternal mortality,[29] and induced abortion.[12]

Strengths and weaknesses of the study

We look at the effects of IPIs following miscarriages, allowing conclusions about how long women should wait after a miscarriage before becoming pregnant again. We replicate the Love et al. study,[7] which also looked at this question, in a very different setting – poor women in rural Bangladesh. Furthermore, we examine the effects of shorter and longer intervals than considered by Love et al. We consider recent data (up to 2008) -- more recent than considered by Love et al. (1981-2000).

The Matlab DSS data on induced abortion and miscarriage are likely to be of high quality and not to suffer from underreporting. In their many years of work in the community the CHWs have established themselves as trustworthy and in a good position to collect reliable information on pregnancy outcomes and, because of their frequent household visits, they are likely to elicit accurate information.[9] Nonetheless, there is probably an under-reporting of early miscarriages since these may not have been identified as pregnancies, and there may be some underreporting of induced abortions and some misreporting of these as miscarriages. Furthermore, the gestation of pregnancy is based on women's reports of the date of their last menstrual period (DLMP), rather than on sonography, which is very rare in Matlab. The reports of DLMP, however, are likely to be quite accurate, since the respondents were visited regularly and the recall periods were relatively short.

The DSS defines a stillbirth as a fetal loss at 28 weeks or longer gestation and miscarriage as a spontaneous fetal loss prior to 28 weeks. Some studies define stillbirth starting at 20 weeks (and Love et al. use a 24-week cutoff), so their definition of stillbirth overlaps with our definition of miscarriage. In our data, for cases for which we know DLMP, there were 50 (of 578) cases where the focal outcome was coded as a miscarriage and the duration of gestation was 20-27 weeks. We are not able to recode these cases, however, because we do not know pregnancy duration for cases for which DLMP is not reported and must rely on the reported outcome of pregnancy 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+- or 24+-week definition.

Though smaller than the sample used by Love et al, our sample (n=10,435) is much larger than that used in other studies of this topic.[4-6 12]

Love et al. found a positive association of the duration of the IPI with the incidence of ectopic pregnancy, caesarean section, preterm delivery, and low birth weight. We either do not have these indicators in our data or have them only for a subsample too small to permit analyses. However, unlike Love et al., for IPIs that end in live births, we look at the mortality of those children during three subperiods of infancy.

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 we find.

Implications for research

This study is of a setting, rural Bangladesh, where fertility and infant mortality rates are relatively high but have fallen considerably over the study period, and one half of the area studied has been exposed to more intense, higher-quality family planning services than are available in many developing countries. The study should be replicated in other settings. Future studies should adjust for the effects of additional potentially confounding variables and assess the effects of the durations of IPIs following miscarriages on the health and survival of the children born at the end of those intervals as well as on those of their mothers. Studies should also assess the effects of IPIs that began with stillbirths and of IPIs that began with induced abortions.

Implications for clinical practice

The current WHO recommendation is that women should wait at least six months after a miscarriage or induced abortion before becoming pregnant again. However, as noted above, that recommendation was based on one study of Latin America of the effects of IPIs following induced *or* spontaneous abortions.[20] Our study, of Matlab, Bangladesh, like that of Love et al. for Scotland,[7] other studies of industrialized countries,[4-6] and a smaller study of Matlab,[12] looks specifically at the effects of IPIs following miscarriages; all of the studies find no higher risk of adverse pregnancy outcomes if women become pregnant soon after a miscarriage. However, we find that very short intervals (≤3 months) following a miscarriage are associated with higher mortality risks for infants in Bangladesh, which suggests that, for the sake of child survival, in less developed settings it may be best for women to wait to at least three months before becoming pregnant again following a miscarriage. Steer noted a similar concern in a 2007 editorial in BJOG.[32]

In developed settings, such as that considered in the Love et al. study, there is concern that postponing pregnancies after a miscarriages may lead to difficulties in conceiving and greater probabilities of miscarriage because of older women's age. This is less of a concern in poor countries such as Bangladesh, where women begin (and often end) childbearing at earlier ages than in more developed countries.

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Contributors: JD conceived the study, oversaw the data analysis, and wrote the paper. LH conducted the data analysis and assisted with the writing of the paper. MR designed the data file construction and assisted with the writing of the paper.

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Ethical approval: Formal ethical review was not necessary for this study because only anonymised data were analyzed. The data file was created based on records of the Matlab Demographic Surveillance System (DSS) of icddr,b. DSS data collection and management procedures are approved by the icddr,b Ethical Review Committee.

Data sharing: No additional data are available. Permission of icddr,b may be sought to use Matlab DSS data for specific research questions.

Table 1. Demographic characteristics of the sample, by Interpregnancy Interval (IPI)

IPI duration	Mother's age at miscarriage at beginning of IPI (s.d.)	Mother's age at outcome at end of IPI (s.d.)	MCH-FP Area (%)	Woman has no education (%)*	Gravida =2 (%)	Year: 1977-1990 (%)	Year: 1991-2000 (%)	Year: 2001-2008 (%)	n
≤3 mos.	24.9 (5.8)	25.6 (5.8)	44.3	51.0	27.7	46.3	25.1	28.6	2,138
3-6 mos.	25.5 (6.1)	26.5 (6.0)	45.1	54.0	23.8	50.2	25.3	24.6	2,458
≤6 mos.	25.2 (6.0)	26.1 (6.0)	44.7	52.6	25.6	48.3	25.1	26.5	4,596
6-12 mos.	25.9 (6.4)	27.2 (6.4)	43.4	53.8	24.4	48.0	27.8	24.1	2,920
12-18 mos.	26.7 (6.7)	28.5 (6.7)	45.9	51.1	21.3	44.5	27.3	28.1	988
18-24 mos.	26.9 (6.8)	29.2 (6.7)	46.8	50.3	21.0	37.9	30.5	31.7	676
>24 mos.	27.0 (6.5)	31.5 (6.5)	46.7	50.0	17.4	29.9	34.3	35.8	1,255
24-36 mos.	27.4 (6.8)	30.5 (6.7)	46.6	50.3	17.4	33.2	32.3	34.5	579
36-48 mos.	27.0 (6.5)	31.1 (6.4)	48.6	45.9	18.8	33.2	29.8	37.0	292
>48 mos.	26.5 (6.0)	33.4 (6.0)	45.3	52.6	16.2	22.4	40.9	36.7	384
Total	25.9 (6.3)	27.5 (6.5)	44.8	52.4	23.5	45.0	27.6	27.4	10,435
Significance of differences across expanded IPI categories	P<0.001	P<0.001	ns	P=0.064	P<0.001	P<0.001	P<0.001	P<0.001	

ns = Not significant

* Among those with non-missing values. Education is not reported for 347 cases.

Table 2. Outcomes of subsequent pregnancy after miscarriage in previous pregnancy, by IPI (n=10,435)

	Outcome of Subsequent Pregnancy						
IPI duration	**Abortion**	**Miscarriage**	**Stillbirth**	**Live Birth**	**Total**	**Col. %**	
≤3 mos.	16	160	87	1,875	2,138	20.5	
(%)	(0.8)	(7.5)	(4.1)	(87.7)	(100.0)		
3-6 mos.	33	262	89	2,074	2,458	23.5	
(%)	(1.3)	(10.7)	(3.6)	(84.4)	(100.0)		
							Love et al. Col. %
≤6 mos.	49	422	176	3,949	4,596	44.0	41.2
(%)	(1.1)	(9.2)	(3.8)	(85.9)	(100.0)		
6-12 mos.	52	302	114	2,452	2,920	28.0	25.2
(%)	(1.8)	(10.3)	(3.9)	(84.0)	(100.0)		
12-18 mos.	25	125	45	793	988	9.5	9.6
(%)	(2.5)	(12.7)	(4.6)	(80.3)	(100.0)		
18-24 mos.	32	81	20	543	676	6.5	6.4
(%)	(4.7)	(12.0)	(3.0)	(80.3)	(100.0)		
>24 mos.	63	173	51	968	1,255	12.0	17.6
(%)	(5.0)	(13.8)	(4.1)	(77.1)	(100.0)		
Total	221	1,103	406	8,705	10,435	100.0	100.0
(%)	(2.1)	(10.6)	(3.9)	(83.4)	(100.0)		
% in Love et al.	(4.9)	(11.7)	(0.6)	(80.3)	(97.5)*		
24-36 mos.	15	66	29	469	578	5.5	
(%)	(2.6)	(11.4)	(5.0)	(81.1)	(100.0)		
36-48 mos.	19	38	9	226	290	2.8	
(%)	(6.5)	(13.1)	(3.1)	(77.9)	(100.0)		
>48	29	69	13	273	384	3.7	
(%)	(7.6)	(18.0)	(3.4)	(71.1)	100.0		

* The Love et al. numbers do not add to 100% because their data also included ectopic pregnancies (0.8% of all outcomes) and "other" outcomes (1.7% of all outcomes).

Table 3. Mortality after miscarriage in previous pregnancy, by IPI among all live births (n=8,705)
(Mortality rates are calculated using denominator for infants alive and in Matlab at the beginning of the interval; 284 migrated out before age 1.)

	Child's age at death						
IPI duration	**First week**	**Week 2-4**	**Week 5-52**	**Known alive at 1 Year**	**Migrated out before Year 1**	**Total births**	**Col. %**
≤3 mos.	67	37	49	1,647	75	1,875	21.5
(%)	(3.6)	(2.0)	(2.6)	(87.8)	(4.0)	(100.0)	
3-6 mos.	64	26	54	1,868	62	2,074	23.8
(%)	(3.1)	(1.3)	(2.6)	(90.1)	(2.9)	(100.0)	
6-12 mos.	81	28	75	2,196	72	2,452	28.2
(%)	(3.3)	(1.1)	(3.1)	(89.6)	(2.9)	(100.0)	
12-18 mos.	31	8	13	714	27	793	9.1
(%)	(3.9)	(1.0)	(1.6)	(90.0)	(3.4)	(100.0)	
18-24 mos.	18	5	12	496	12	543	6.2
(%)	(3.3)	(0.9)	(2.2)	(91.3)	(2.2)	(100.0)	
24-36 mos.	16	2	7	438	16	469	5.4
(%)	(3.4)	(0.4)	(1.5)	(93.4)	(3.4)	(100.0)	
36-48 mos.	6	2	6	207	5	226	2.6
(%)	(2.7)	(0.8)	(2.7)	(91.5)	(2.2)	(100.0)	
>48	9	2	4	243	15	273	3.1
(%)	(3.3)	(0.7)	(1.5)	(89.0)	(5.5)	(100.0)	
Total	292	110	220	7,799	284	8,705	
(%)	(3.4)	(1.3)	(2.5)	(89.5)	(3.6)	100.0	
Rate per 1,000 at risk	33.5	13.1	26.6				

Figure 1. Relative risk ratios of induced abortion, miscarriage, and stillbirth following a miscarriage by IPI duration: unadjusted and adjusted results from Matlab and Love et al. (2010) (Note: Solid symbols indicate p <0.05)

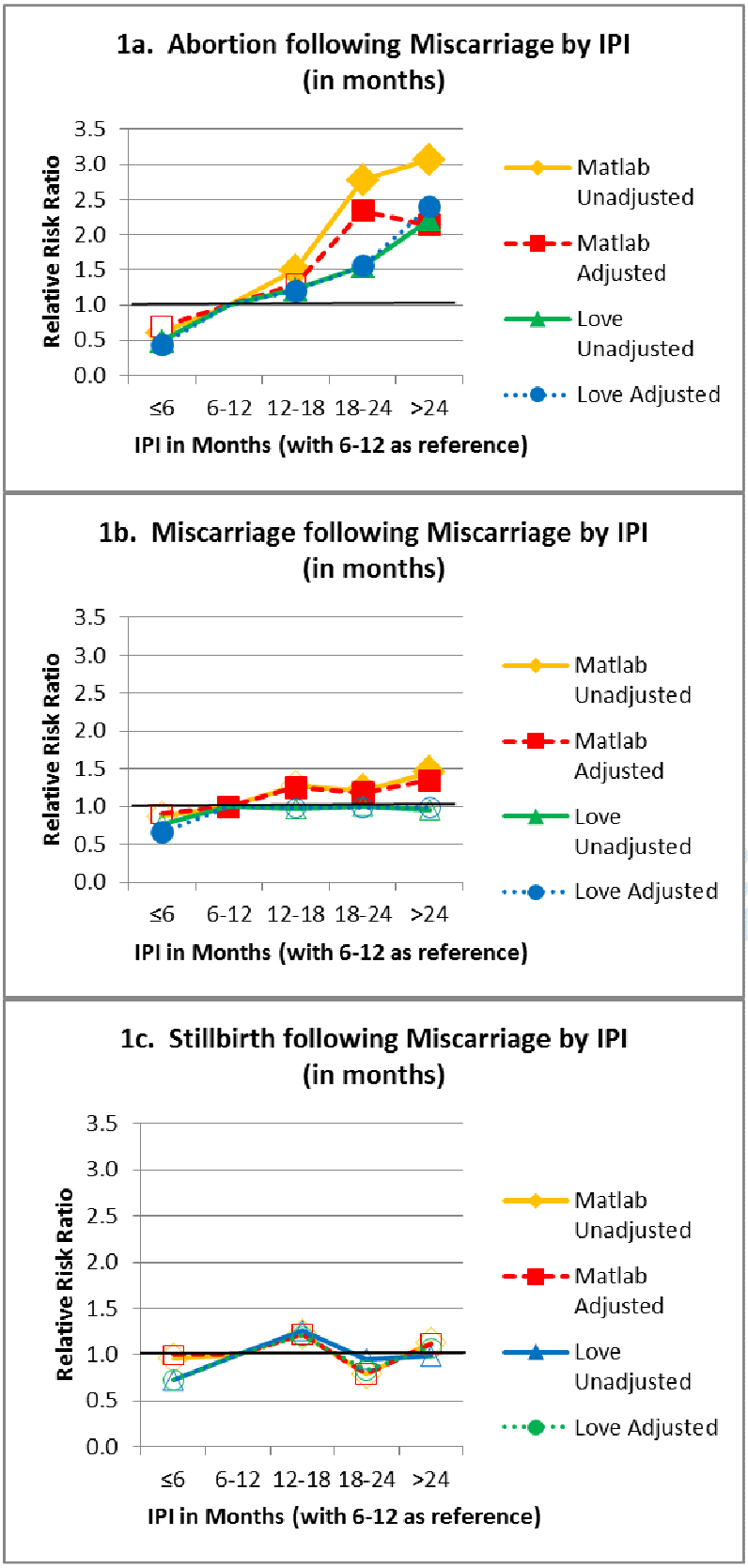


Figure 2. Relative risk ratios of induced abortion, miscarriage, and stillbirth following a miscarriage by expanded IPI categories: unadjusted and adjusted results for Matlab
(Note: Solid symbols indicate p <0.05)

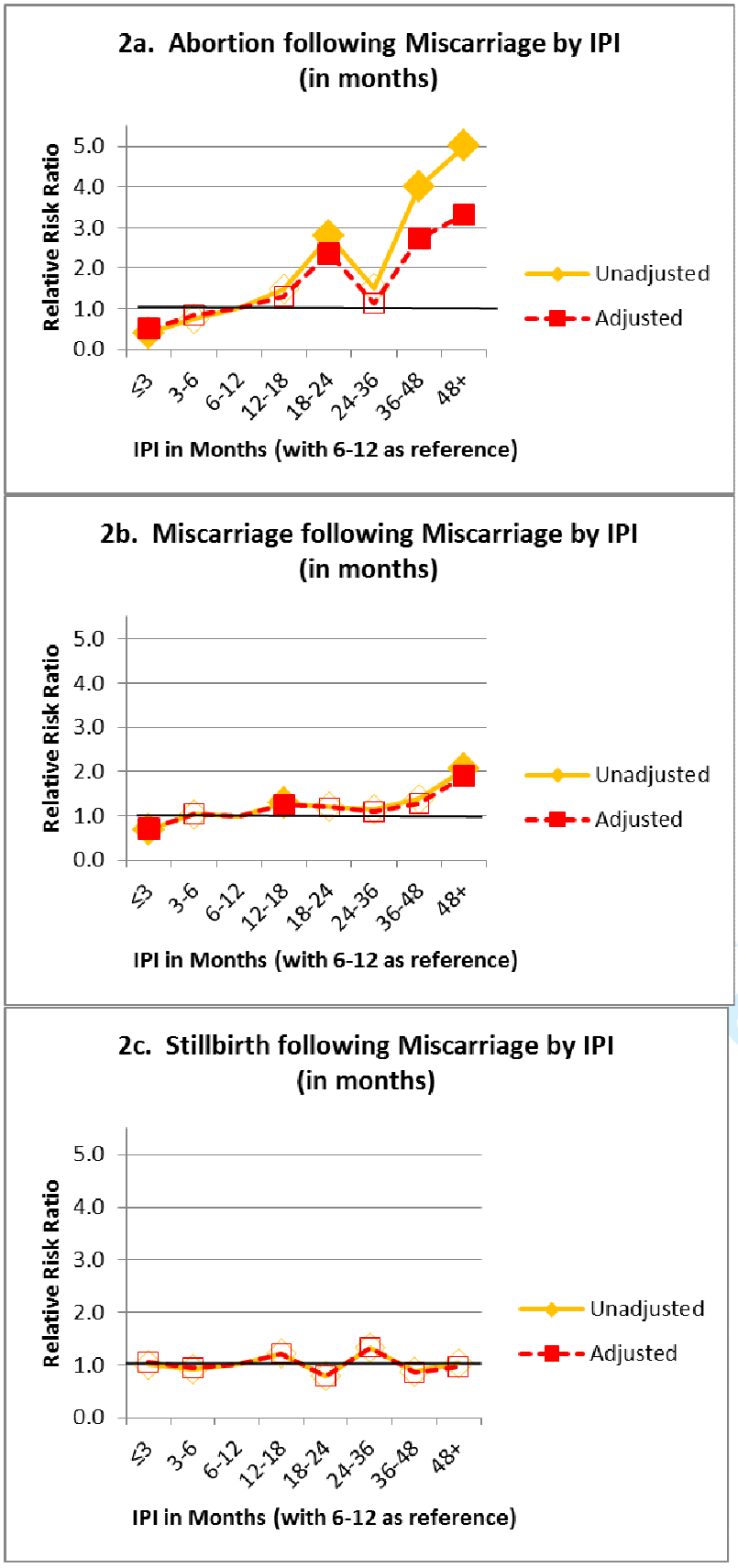
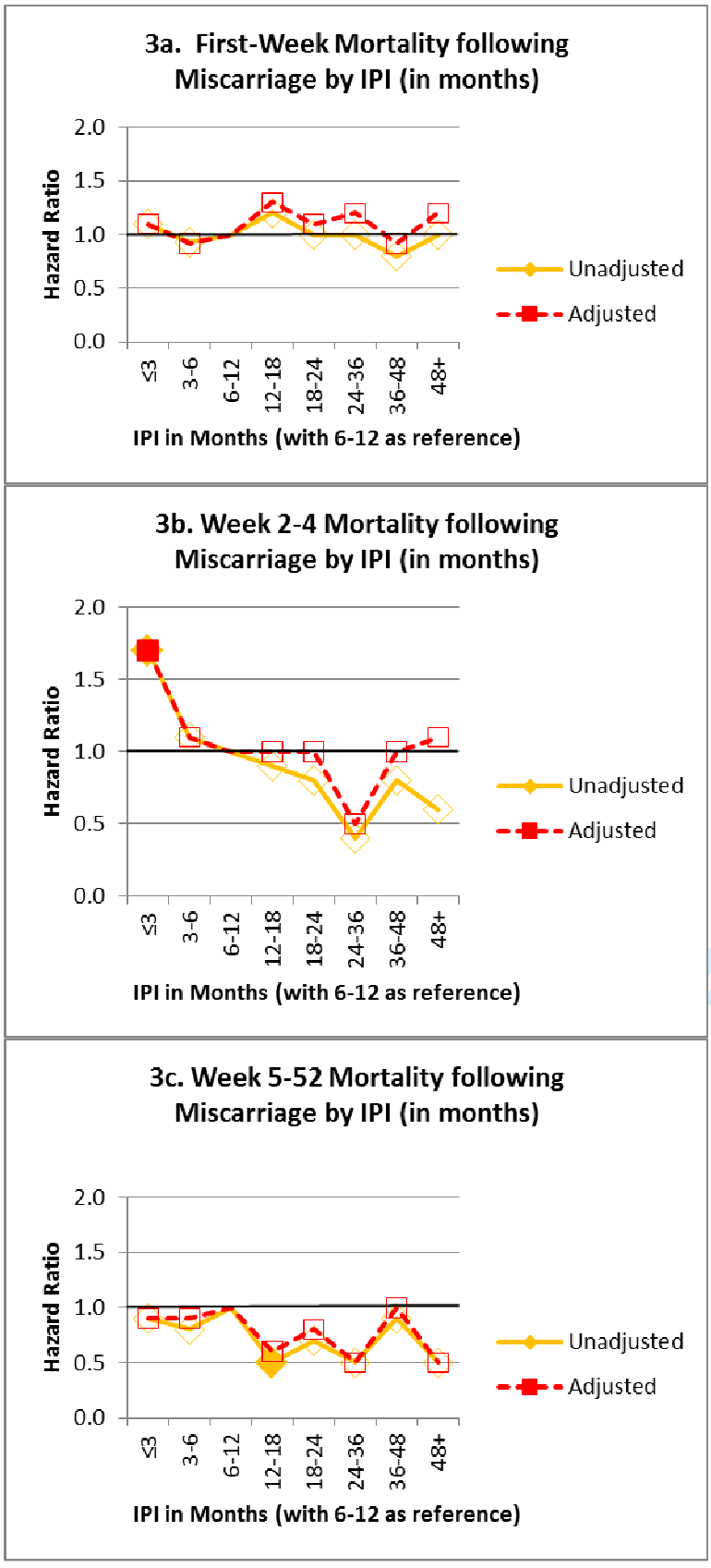


Figure 3. Hazard ratios of mortality during subperiods of infancy, by IPI duration, unadjusted and adjusted results from Matlab (Note: Solid symbols indicate p <0.05)



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The Effects of Pregnancy Spacing After a Miscarriage on Subsequent Pregnancy Outcomes: Evidence from Matlab, Bangladesh

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ABSTRACT

Objective To determine the optimum interpregnancy interval following a miscarriage and to see if findings for a poor, rural area in Bangladesh are similar to those in a recent study of Scottish women.

Design Multivariate analysis of population-based, prospective data from a demographic surveillance system (study cohort).

Setting Pregnancies in Matlab, Bangladesh, between 1977 and 2008.

Participants 9,214 women with 10,453 pregnancies that ended in a miscarriage and were followed by another pregnancy outcome.

Main outcome measures Outcome of pregnancy following the miscarriage was singleton live birth, stillbirth, miscarriage, or induced abortion. For pregnancies that ended in live birth, whether the child died in first week of life, in the next three weeks, or between 29 days and one year of age.

Results Compared with interpregnancy intervals (IPIs) of 6-12 months, pregnancies that were conceived less than three months after a miscarriage were more likely to result in a live birth and less likely to result in a miscarriage (adjusted odds ratio 0.70, 95% confidence interval 0.57 to 0.86) or induced abortion (0.50, 0.29 to 0.89). Induced abortions were significantly more likely following IPIs of 18-24 months (2.36, 1.48 to 3.76), 36-48 months (2.73, 1.50 to 4.94), and more than 48 months (3.32, 1.68 to 2.95), and miscarriages were more likely following IPIs of 12-17 months (1.25, 1.01 to 1.56) and more than 48 months (1.90, 1.40 to 2.58). No significant effects of IPI duration are seen on the risks of a stillbirth. These results are remarkably similar to those in a recent analysis of a large sample of Scottish women. However, we find a different pattern when we consider whether the infant born at the end of the IPI died: Compared to IPIs of 6-12 months, the shortest IPIs following a miscarriage (≤3 months) are associated with significantly higher late neonatal mortality (adjusted relative risk ratio 1.74, 1.06 to 2.84), and IPIs of 12-18 months are associated with a significantly lower unadjusted risk of post-neonatal mortality (0.54, 0.30 to 0.96).

Conclusions The shorter the IPI following a miscarriage, the more likely the subsequent pregnancy is to result in a live birth. However, very short IPIs may not be advisable in poor countries like Bangladesh because they are associated with a higher risk of mortality for the infants born after them.

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WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

Most previous studies of the effects of pregnancy spacing have considered intervals following live births

A recent study of Scottish women finds that after an initial miscarriage, women had the best pregnancy outcomes if they conceived again within six months and the worst outcomes if they didn't conceive until at least 24 months after the miscarriage

It is not known whether this is also true for women in poor, developing countries or whether the duration of the IPI following a miscarriage affects infant mortality

WHAT THIS STUDY ADDS

As was found in the study of Scottish women, after a miscarriage Bangladeshi women were most likely to have a live birth (compared to another type of pregnancy outcome) if they conceived again within six months and least likely if they did not conceive until at least 24 months after the miscarriage

In Bangladesh, pregnancy outcomes after a miscarriage were best for even shorter intervals (≤3 months) than considered in the Scottish study and worst for even longer intervals (>48 months)

However, patterns are different for infant survival outcomes: Compared to intervals of 6-12 months, the shortest intervals following a miscarriage (≤3 months) are associated with significantly higher unadjusted and adjusted risks of late neonatal mortality, and intervals of 12-18 months are associated with a significantly lower unadjusted risk of post-neonatal mortality

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INTRODUCTION

Many studies have addressed the effect on maternal[1] and perinatal[2] outcomes and on infant and child mortality[3] of pregnancy spacing following a live birth or following a live birth or stillbirth. However, very few studies have sought to identify the optimum interpregnancy interval (IPI) following a miscarriage (spontaneous abortion); the studies that have been done are generally of women living in industrialized countries, and most have relatively small sample sizes.[4 5 6] An article by Love et al. published in this journal in 2010[7] considered a large sample of women who delivered in Scottish hospitals to look at the effects of IPIs that began with a miscarriage. The study found that women who conceived within six months after a miscarriage had better outcomes of the subsequent pregnancy than women who waited longer to conceive again; e.g., they were less likely to have a voluntary pregnancy termination (induced abortion) or another miscarriage. In this paper we investigate whether these same findings are seen in a very different setting – among poor women in rural Bangladesh. We also investigate whether infants born at the ends of the intervals died before their first birthday. Women in Bangladesh are more likely to be malnourished than those in industrialized countries,[8] and hence may be more likely to be nutritionally depleted by a pregnancy, even one that ends in miscarriage.

METHODS

We use high-quality longitudinal data from the Matlab Demographic Surveillance System (DSS). Matlab is a rural sub-district of Bangladesh that is well known for its DSS and its Maternal Child Heath-Family Planning (MCH-FP) project, which operates in half of the area covered by the DSS to provide intensive and quality family planning and maternal/child health services.[9,10,11] The other half, known as Comparison Area, is typical of much of Bangladesh in contraceptive use,[12] fertility and childhood mortality,[13] and maternal mortality.[14] The MCH-FP Area has lower fertility rates[15] and lower rates of induced abortion,[16] miscarriage,[17] and stillbirth,[18] and greater coverage of antenatal care and better access to basic and emergency obstetric care than the Comparison Area.[15 18]

The Matlab DSS contains, for both areas of Matlab, longitudinal records of pregnancy outcomes and deaths for all household members. During their regular visits to each household, fortnightly between 1966 and 1999, monthly between 2000 and 2006, and bimonthly since 2007, the community health workers (CHWs) record pregnancy status at the time of the visit and any pregnancy outcomes or household deaths that occurred prior to the visit.

The DSS provides information on 245,091 pregnancies that occurred between 1974 and 2008. In this study we consider the 10,435 pregnancies documented in the DSS that began with a miscarriage in January 1977 or later and were followed by another pregnancy outcome (here called the "focal pregnancy") other than a multiple live birth not later than December 2008. Before 1977, the DSS did not distinguish between spontaneous and induced abortions. In the DSS, a miscarriage (spontaneous abortion) is defined as a spontaneous fetal loss prior to 28 weeks gestation. We exclude from the sample focal pregnancies that ended with multiple live births; 246 pregnancies are excluded for this reason.

We consider the following outcomes of the focal pregnancies that follow the IPI after a miscarriage: singleton live birth, stillbirth, miscarriage, and induced abortion. In the DSS, a *live birth* is the delivery of a live baby at any gestational age; a *stillbirth* is a fetal loss at 28 weeks or longer gestation; as noted above, a spontaneous abortion, or *miscarriage*, is a spontaneous fetal loss prior to 28 weeks; and induced abortion is self-reported. Early-gestation pregnancy termination is legal in Bangladesh if performed in a medical setting before the pregnancy is clinically confirmed. Such pregnancy terminations are done by manual vacuum aspiration by trained female paramedics at the government Health and Family Welfare Centers and are known as "menstrual regulation," or "MR.". MR can be performed only within 10 weeks of the last menstrual period before pregnancy is clinically confirmed. MR has been available through government and other medical facilities in Bangladesh since the late 1970s, when the government

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agreed to permit such pregnancy terminations in an effort to replace the practice of unsafe abortion. Pregnancy termination in a non-medical setting or after pregnancy is clinically confirmed is prohibited in Bangladesh except when done to save a woman's life. Our "induced abortion" category includes both MRs and voluntary pregnancy terminations by other means. (Method of pregnancy termination has been distinguished in the DSS since 1989. Since then, 52% of terminations have been by MR, 3% by D&C, and 45% by other means.)

We also consider mortality of the children born in the focal pregnancies during three subperiods of the child's first year of life – early neonatal (first week of life), late neonatal (next three weeks of life), and post-neonatal (the rest of the first year of life). The sample for our analyses of early neonatal mortality is the 8,705 pregnancy intervals that began with a miscarriage and ended with a live birth. The sample for late neonatal mortality is the 8,401 of these that survived the first week of life and were still living in Matlab, and the sample for post-neonatal mortality is the 8,268 of these that survived the first four weeks of life and were still living in Matlab.

The duration of the IPI is defined by measuring the amount of time between the preceding miscarriage and the estimated date of conception of the focal pregnancy. For the 5,914 cases for which we know the date of the last menstrual period (DLMP), we estimate the date of conception as occurring two weeks after the DLMP before the focal pregnancy. For the 4,519 cases for which DLMP was not reported, we estimate the duration of the IPI as the amount of time between the miscarriage and the end of the focal pregnancy less the estimated duration of the focal pregnancy, based on the outcome of that focal pregnancy. Our estimate of duration of each type of pregnancy outcome is the average duration of all pregnancies that ended with that outcome for which we know DLMP. These averages are 36 weeks for live births, 33 weeks for stillbirths, 11 weeks for miscarriages, and 8 weeks for induced abortions. We have also done all analyses only for the cases for which DLMP was reported, and the sizes of the odds ratios and relative risks are similar to those reported here.

Our multivariate analyses control for the woman's age at the time of the focal outcome (with a series of dichotomous indicators [age < 20, 20-24, 25-29, 30-34, 35-39, and 40+] to allow for non-linear effects), a proxy for socioeconomic status (the woman's educational attainment), and calendar year (approximately 10-year bands of the calendar year of the focal outcome). (We used interactions to explore whether the IPI effects varied over time, but these were never statistically significant.) We also control for the gravidity of the focal pregnancy and for whether the woman lived in the MCH-FP Area or the Comparison Area of Matlab. Data on maternal age, gravidity, area, and calendar year all come from the DSS. Information on women's education is from periodic censuses conducted by ICDDR,B in the Matlab area. Most of the potential confounders vary significantly with IPI, as can be seen in Table 1. Women's ages at both the beginnings and ends of the IPI are positively related to IPI duration, and longer IPIs are more likely to be for higher gravidity and to occur in the later years covered by the data.

Statistical analysis

We assess the effects of the duration of the IPI on the outcome of the subsequent pregnancy with crude and adjusted odds ratios that derive from univariate and multivariate multinomial logistic regressions. The effects of IPI duration on mortality during subperiods of infancy are estimated with Cox proportional hazards models. All models are estimated by Stata 11.0. The hazard model allows for censoring due to moving out of the Matlab area or not completing the at-risk period by the end of 2008. The multivariate analyses control for the variables mentioned above. We used the cluster command in Stata 11.0 to adjust standard errors for the fact that we have more than one pregnancy for some women. Of the women in our sample, 7,698 are represented once, and 1,516 have more than one observation (i.e., had more than one miscarriage that was followed by another pregnancy outcome).

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To facilitate comparisons we consider the same categories of IPI durations considered by Love et al. -- ≤6 months (0 to 24 weeks), 6-12, months (25-52 weeks) (reference category), 12-18 months (53 -76 weeks), 18-24 months (77-104 weeks), and >24 months (105 or more weeks), where each category includes the upper bound but not the lower bound. We also conduct analyses that consider additional categories of IPIs, breaking the ≤6 months category into ≤3 months (0-12 weeks) and 4-6 months (13 -24 weeks) to assess the effects of very short intervals, and breaking the >24 months category into 24-36 months, 36-48 months, and >48 months, since other studies have found different effects of such longer intervals.[19]

RESULTS

The middle of Table 2 shows the cross-tabulation of IPI duration and outcome of the focal pregnancy for the IPI categories considered by Love et al. The rows above that show the finer breakdown of the ≤6 months category, and the rows below that show the finer breakdown of the >24 months category. Of the 10,435 cases in our sample, 4,596 (44.0%) conceived 6 months or less after the miscarriage (20.5% within 3 months or less and 23.5% in 4-6 months). The next largest percentage is for IPIs of 6-12 months (28.0%). The percentages for IPIs of 12-18 and 18-24 months are 9.5% and 6.5%, respectively. IPIs longer than 24 months comprise 12.0% of the sample (5.5% are 24-36 months long, 2.8% are 36-48 months, and 3.7% are longer than 48 months). We find a somewhat higher incidence of short intervals (of 12 months or less) and a somewhat lower incidence of long intervals (more than 24 months) than Love et al. find for Scottish women, but the IPI distributions are generally fairly similar, as can be seen in the right-hand column of Table 2.

Of all IPIs that began with a miscarriage, 2.1% ended with an induced abortion, 10.6% ended with another miscarriage, 3.9% ended with a stillbirth, and 83.4% ended with a live birth (Table 2). The percentage of post-miscarriage pregnancies that end with a live birth decreases as the length of the IPI increases. It is highest for the shortest IPIs (85.9% for IPI ≤6 months and 87.7% for IPI ≤3 months) and lowest for the longest IPIs (77.1% for IPI >24 months and 71.1% for IPI >48 months). The percentages for induced abortion and miscarriage each increase nearly monotonically as IPI increases, but there is little systematic pattern for stillbirths. A similar pattern was found for Scottish women, as can be seen in Table 2, though the incidence of stillbirth is lower in their data and the incidence of induced abortion higher than we find for Matlab, Bangladesh.

Of all IPIs that began with a miscarriage and ended with a live birth, 292 of those live-born children died in their first week of life (33.5 early neonatal deaths per 1,000 live births). Of those who survived the first week, 13.1/1,000 died in the next three weeks. And of those who survived the first four weeks, 26.6/1,000 died before their first birthday (Table 3). The patterns of how mortality varies with duration of IPI are not a smooth as those for pregnancy outcomes, but they show that the risks of mortality are often higher for the shorter IPIs and lower for the longer IPIs. The percentage of babies known to be alive at one year is below the sample average for IPI ≤3 months and above the sample average for all IPI categories of longer than 3 months and less than 36 months.

Figure 1 shows the unadjusted and adjusted odds ratios of the outcome of the focal pregnancy in our data and how they compare to those found by Love et al. for Scottish women. The patterns are quite similar in the two studies. In both studies, no significant effects of IPI duration are seen on the risks of a stillbirth, but the unadjusted odds of induced abortion increase monotonically as IPI duration increases, being lowest for IPIs of less than 6 months (for Matlab unadjusted OR for IPI ≤6 months = 0.59, 95% confidence interval 0.40 to 0.86, relative to IPI=6-12 months) and highest for IPIs of at least 24 months (for Matlab unadjusted OR= 3.07 [2.11 to 4.46] relative to IPI=6-12 months). In Matlab, the unadjusted odds of a subsequent miscarriage also generally increase with IPI duration, being highest for IPIs of at least 24 months, whereas in Scotland long IPIs are not associated with higher odds of miscarriage. For both induced abortion

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and miscarriage, the patterns are very similar in the two studies for the shortest IPIs, but the pernicious effects of long intervals on the unadjusted odds are larger for Matlab than in Scotland. Adjusting for other variables generally has more effect in our data from Matlab than it did in Love et al.'s data from Scotland. In the Matlab data, the effect of adjustment is greatest for the longest intervals, so much so that the adjusted odds ratio for IPIs of at least 24 months on induced abortion is slightly lower for Matlab than for Scotland.

Figure 2 shows unadjusted and adjusted odds ratios of the outcome of the focal pregnancy for our finer breakdown of IPI categories. It shows that the same patterns persist *within* the IPI ≤6 months and IPI >24 months categories, though the odds of a live birth for 24-36 months are lower than those for 18-24 months. Pregnancies that were conceived less than three months after a miscarriage were the most likely to result in a live birth and least likely to result in a miscarriage (adjusted odds ratio 0.70, 95% confidence interval 0.59 to 0.86, relative to IPI=6-12 months) or induced abortion (0.50, 0.29 to 0.89). Induced abortions were more likely following IPIs of 18-24 months (2.36, 1.48 to 3.75), 36-48 months (2.73, 1.50 to 4.94), and more than 48 months (3.32, 2.05 to 5.38); and miscarriages were more likely following IPIs of 12-17 months (1.25, 1.01 to 1.56) and more than 48 months (1.90, 1.40 to 2.58). Again, adjustment has a greater effect the longer the IPI. Again, no significant effects of IPI duration are seen on the risks of a stillbirth.

Figure 3 shows the hazard ratios of mortality during the three subperiods of infancy for our finer breakdown of IPI categories. We find no significant relationships between IPI duration and early neonatal mortality in either our unadjusted or adjusted analyses. However, for late neonatal mortality, in both the unadjusted and the adjusted analyses, we find significantly higher risk of mortality for IPIs ≤ 3 months (adjusted relative risk ratio 1.74, 1.06 to 2.84) and generally see a decline in mortality as IPI duration increases up to 36 months. We find a significantly lower unadjusted risk of post-neonatal mortality (between the 5th and 52nd week of life) for IPIs of 12-18 months compared to those of 6-12 months (0.54, 0.30 to 0.96). (The adjusted risk ratio is similar but is not statistically significant [0.56, 0.31 to 1.01].)

DISCUSSION

We find that the shorter IPI following a miscarriage, the more likely the subsequent pregnancy is to result in a live birth. Women with IPIs of at least 18 months following a miscarriage, and especially those with intervals of at least 48 months have a much higher likelihood of experiencing another miscarriage or having an induced abortion. The odds of an induced abortion following a miscarriage are particularly high for the longest IPI category (unadjusted OR for IPI>48 months = 5.02 [3.13 to 8.03] and adjusted OR = 3.32 [2.05 to 5.38]). Adjusting for the effects of demographic and socioeconomic variables reduces the effect of long intervals on induced abortion, but they remain large and significant. No significant effects of IPI duration are seen on the risks of a stillbirth.

However, we see quite different patterns when we consider the effect of pregnancy spacing after a miscarriage on early and late neonatal and post-neonatal mortality. Compared to IPIs of 6-12 months, the shortest IPIs following a miscarriage (≤3 months) are associated with significantly higher unadjusted and adjusted risks of late neonatal mortality, and IPIs of 12-18 months are associated with a significantly lower unadjusted risk of post-neonatal mortality. Hence, we find some evidence that short IPIs are associated with higher mortality between the first week and the end of the first year of life for the children born after a miscarriage. It appears that children born after very short IPIs following a miscarriage are able to survive the first week of life but then are at higher risk of dying in the rest of the first year.

Comparison to other studies

Most studies of the effects of pregnancy spacing consider intervals that began with a live birth or with a live birth or stillbirth.[1-3 20] They generally find adverse effects of both short and long

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intervals, but the "optimum" interval (the one with the lowest risk of an adverse outcome) differs across types of outcomes. For example, a study of the U.S. that considers intervals that began with live births finds the lowest risks of adverse perinatal outcomes for IPIs of 18-23 months duration.[21] A meta-analysis of the effects of intervals following live births on perinatal outcomes found that intervals of 18-59 months are associated with better outcomes than shorter and longer intervals,[2] and a review of studies of maternal outcomes reaches a similar conclusion.[1] An analysis of data from a number of developing countries found infant mortality to be lowest for intervals of at least 24 months duration that began with live births, and under-five mortality to be lowest for intervals of at least 36 months.[3]

A study of the Matlab MCH-FP Area found that following live births the risks of miscarriage and of stillbirth in the next pregnancy were significantly higher for IPIs shorter than 6 months (compared to those of 27-50 months duration).[19] That study did not distinguish the type of outcome that began IPIs longer than 50 months, but most of such longer IPIs began with a live birth and the likelihoods of miscarriage and of stillbirth were also significantly higher for IPIs of 75 months or longer compared to those of 27-50 months that began with a live birth. Two earlier studies in Bangladesh, however, found no relationship between late fetal death (after 28 weeks of gestation) and short IPIs (<12 months) compared with intervals longer than 24 months.[22 23] Studies using data from Sweden found that very short (0–3 months) IPIs following live births were associated with higher risks of stillbirth.[24 25] Studies of World Fertility Survey data from a number of developing countries found IPIs of less than 9 months following live births to be associated with higher risks of fetal death;[26 27] early fetal losses and stillbirths were combined in those studies.

We consider intervals that began with a miscarriage, in essence asking the question "How long after a miscarriage should a woman wait before becoming pregnant again?" There are very few studies that look specifically at IPIs that began with a miscarriage.

A study of Latin America that assessed the effects of intervals following induced and spontaneous abortions found that intervals shorter than six months between abortion and subsequent pregnancy were associated with elevated risks of premature rupturing of membranes, anemia and bleeding, pre-term and very pre-term births, and low birthweight, compared with longer intervals.[28] However, that study was not able to distinguish between induced and spontaneous abortions. 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. WHO currently recommends "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."[29] This recommendation is based on the study of Latin America just mentioned.[28] The report on the WHO Technical Consultation that makes that recommendation also recommends "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).[29]

Three studies[4-6] using data from the U.S. or Europe find no effects of the duration of IPI following a miscarriage on the outcome of the subsequent pregnancy, but their samples are relatively small (64, 91, and 1,530 respectively). An earlier study of Matlab that considered a much smaller sample of IPIs that began with a miscarriage than that considered here and only in the MCH-FP Area also found, like we do here, a decreasing likelihood of having a live birth following a miscarriage as duration of the preceding IPI increases.[19]

Love et al.'s recent study uses a large sample of pregnancies to Scottish women who had a miscarriage to assess the effects of pregnancy spacing of the outcome of the subsequent pregnancy.[7] We have constructed our analyses to be as similar as possible to those of Love et al. to facilitate comparisons. Our results for pregnancy outcomes are remarkably similar to theirs. Both studies find that short IPIs following a miscarriage are associated with lower risks of a

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subsequent miscarriage or an induced abortion, and long intervals are associated with higher risks of these outcomes, and both find no significant effects of the duration of the IPI following a miscarriage on the risk of stillbirth.

We also examine even shorter and longer IPIs durations than Love et al. do and show that the very shortest intervals we consider (≤ 3 months) are associated with the lowest risks of induced abortion and miscarriage and the longest (>48 months) are associated with the highest risks of these outcomes. For example, for the likelihood of another miscarriage, we do not see the significant "beneficial" effect of IPI ≤6 months (relative to IPI = 6-12 months) found by Love et al., but we do see a beneficial effect when we consider IPI ≤3 months (adjusted odds ratio 0.70, 95% confidence interval 0.57 to 0.86).

We generally find even stronger pernicious effects of long intervals on the odds of a miscarriage or an induced abortion in the focal pregnancy than was found for Scottish women, and the effects are particularly large when we consider an expanded set of IPI categories (up to >48 months). Adjusting for the effects of demographic and socioeconomic variables reduces the effects of long intervals on the likelihood of induced abortion more for Matlab than it did in Love et al.'s study of Scotland; the adjusted risk associated with intervals of more than 24 months (compared to those of 6-12 months) is slightly lower for Matlab than those Love et al. found for Scotland (whereas the opposite is true for unadjusted risks). 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 subsample and found patterns similar to those reported here, but they were not statistically significant.

We find some evidence that short IPIs following miscarriages are associated with higher mortality between the first week and the end of the first year of life for the children born after a miscarriage. Another study of Matlab found that short inter-outcome intervals (less than 15 months between one pregnancy outcome and the next outcome) that began with a miscarriage were associated with higher risks of early and late neonatal mortality compared with intervals of 36-59 months that began with the live birth of a child who survived.[30] (However, that study did not compare them to longer inter-outcome intervals that began with a miscarriage.) By contrast Love et al. do not find short IPIs to be associated with higher risks of preterm delivery and low birthweight – outcomes that have been widely found to be associated with mortality during infancy.[31 32] The better nutritional status of Scottish women may buffer their fetuses from the depleting effects of a recent previous miscarriage.

Previous studies have offered a number of hypotheses to explain the effects of IPIs on maternal, perinatal, and infant and child health outcomes. The main hypotheses offered to explain why there might be adverse effects of short IPIs are (1) competition for family resources and time from a just-older sibling;[30] (2) transmission of infection among closely-spaced siblings ;[30] and (3) maternal depletion,[33] especially of folate.[34] The first and second mechanisms would only come into play for intervals that began with live births of children who survived, and clearly do not apply to our case of IPIs that began with miscarriages. Maternal depletion is more likely the longer the pregnancy (and, if the pregnancy results in the live birth of a child who survives, breastfeeding, especially if unsupplemented, can further deplete the woman).[33] Folate depletion begins around 5 months gestation.[34] Since our definition of miscarriages includes pregnancies up to 28 weeks gestation, some of the pregnancies could lead to folate depletion. 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

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The decreasing likelihood of having a live birth following a miscarriage as duration of the preceding IPI increases is consistent with what we found in an earlier study of Matlab that considered a much smaller sample of IPIs that began with a miscarriage than that considered here.[15] ¶
Our findings for Bangladesh, like those of Love et al. for Scotland, are consistent with the notion that most women who had a miscarriage wanted to have a live birth, and as a result many of them seek to become pregnant again as soon as possible. Over a fifth (20.5%) of the women in our sample who experienced a miscarriage and became pregnant again did so within three months of the miscarriage, and nearly half (44.0%) were pregnant within six months. ¶
We generally find even stronger pernicious effects of long intervals on the odds of an induced abortion or miscarriage in the focal pregnancy than Love et al. did, and the effects are particularly large when we consider an expanded set of IPI categories (up to >48 months). This suggests not only that women in Matlab do not want to have long intervals, but also those who do may be selective of women in poorer health who take longer to conceive. 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 interval similar to first pregnancies,[17] which have been shown to have higher risk of many poor outcomes.[18] A meta-analysis has shown that IPIs longer than 59 months are associated with adverse perinatal outcomes.[19] Other studies of Matlab have shown that women with long intervals (but not distinguishing the type of outcome with which they began) have higher risks of pregnancy complications,[20] maternal mortality,[21] and induced abortion.[15]

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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.[35]

Our finding that short IPIs following a miscarriage are associated with a higher likelihood of a live birth at the end of the interval is consistent with the notion that most women who had a miscarriage wanted to have a live birth, and as a result many of them seek to become pregnant again as soon as possible and may take very good care of themselves during the subsequent pregnancy. A fifth (20.5%) of the women in our sample who experienced a miscarriage and became pregnant again did so within three months of the miscarriage, and nearly half (44.0%) were pregnant within six months.

To explain the adverse effects of long IPIs on pregnancy outcomes, it has 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,[21] which have been shown to have higher risk of many poor outcomes.[36] It is also possible that long intervals are selective of women in poorer health, who take longer to conceive ,[37] or that women who have long intervals did not want to become pregnant again and do not take as good care of themselves during pregnancy.[19] In addition, long IPIs are more likely for older women; older maternal age is associated with its own independent adverse effects on pregnancy outcomes,[38] though we see an effect even when we control for maternal age. A meta-analysis has shown that IPIs longer than 59 months are associated with adverse perinatal outcomes.[19] That study also found adverse effects on perinatal outcomes of intervals shorter than 18 months, which we do not see for pregnancy outcomes, but we do see some adverse effects of very short intervals on infant survival. Other studies of Matlab have shown that women with long intervals (but not distinguishing the type of outcome with which they began) have higher risks of pregnancy complications,[39] maternal mortality,[37] and induced abortion.[19]

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Strengths and weaknesses of the study

We look at the effects of IPIs following miscarriages, allowing conclusions about how long women should wait after a miscarriage before becoming pregnant again. We replicate the Love et al. study,[7] which also looked at this question, in a very different setting – poor women in rural Bangladesh. Furthermore, we examine the effects of shorter and longer intervals than considered by Love et al. We consider recent data (up to 2008) -- more recent than those considered in the Love et al. study (which covered the period 1981-2000).

The Matlab DSS data on induced and spontaneous abortion (miscarriage) are likely to be of high quality and not to suffer from underreporting. In their many years of work in the community the CHWs have established themselves as trustworthy and in a good position to collect reliable information on pregnancy outcomes and, because of their frequent household visits, they are likely to elicit accurate information.[9] Nonetheless, there is probably an under-reporting of early miscarriages since these may not have been identified as pregnancies, and there may be some underreporting of voluntary pregnancy terminations and some misreporting of such terminations as miscarriages. Furthermore, the gestation of pregnancy is based on women's reports of the date of their last menstrual period (DLMP), rather than on sonography, which is very rare in Matlab. The reports of DLMP, however, are likely to be quite accurate, since the respondents were visited regularly and the recall periods were relatively short.

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The DSS defines a *stillbirth* as a fetal loss at 28 weeks or longer gestation and spontaneous abortion, or *miscarriage*, is a spontaneous fetal loss prior to 28 weeks. Some studies define stillbirth starting at 20+ weeks (and Love et al. use a 24-week cutoff), so their definition of stillbirth overlaps with our definition of miscarriage. In our data, for cases for which we know DLMP, there were 50 (of 578) cases where the focal outcome was coded as a miscarriage and the duration of gestation was 20-27 weeks. We are not able to recode these cases because we do not know pregnancy duration for cases for which DLMP is not reported and must rely on the reported outcome of pregnancy for those cases. The fact that we find no evidence of maternal depletion on

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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+- or 24+-week definition.

Though smaller than the sample used by Love et al, our sample (n=10,435) is much larger than that used in other studies of this topic.[4-6 19]

We consider effects of IPI after a miscarriage on pregnancy outcomes – live birth, stillbirth, miscarriage, and induced abortion – but we are not able to look at ectopic pregnancies as Love et al. do. They found a positive association of the duration of the IPI with the incidence of ectopic pregnancy, and also with caesarean section, preterm delivery, and low birth weight. We either do not have these indicators in our data or have them only for a subsample too small to permit analyses. However, unlike Love et al., for IPIs that end in live births, we look at the mortality of those children during three subperiods of infancy.

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.

Implications for research

This study is of a setting, in rural Bangladesh, with fertility and infant mortality rates that are relatively high but have fallen considerably over the study period, and one half of the area studied has been exposed to more intense, higher-quality family planning services than are available in many developing countries. The study should be replicated in other settings. Future studies should adjust for the effects of additional potentially confounding variables (such as those mentioned above) and should assess the effects of the durations of IPIs following miscarriages on the health and survival of the children born at the end of those intervals as well as on those of their mothers. Studies should also assess the effects of IPIs that began with stillbirths and of IPIs that began with induced abortions, and they should investigate the influence of the duration of pregnancy gestation at the time of the fetal loss.

Implications for clinical practice

The current WHO recommendation is that women should wait at least six months after a miscarriage or induced abortion before becoming pregnant again. However, as noted above, that recommendation was based on one study of Latin America of the effects of IPIs following induced *or* spontaneous abortions.[28] Our study, of Matlab, Bangladesh, like that of Love et al. for Scotland,[7] other studies of industrialized countries,[4-6] and a smaller study of Matlab,[19] looks specifically at the effects of IPIs following miscarriages, and all of the studies find no higher risk of adverse pregnancy outcomes if women become pregnant soon after a miscarriage. However, we find that very short intervals (< 3 months) following a miscarriage are associated with higher mortality risks for infants in Bangladesh, which suggests that, for the sake of child survival, in less developed settings it may be best for women to wait to at least three months before becoming pregnant again following as miscarriage. Steer noted a similar concern in a 2007 editorial in BJOG.[40]

In developed settings, such as that considered in the Love et al. study, there is concern that postponing pregnancies after a miscarriages may lead to difficulties in conceiving and greater probabilities of miscarriage because of older women's age. This is less of a concern in poor countries such as Bangladesh, where women begin (and often end) childbearing at earlier ages than in more developed countries.

Conclusion

Women who conceive within three months of a miscarriage are more likely to have the subsequent pregnancy result in a live birth. However, the children born after IPIs that began with a miscarriage are more likely to die in infancy if the IPI was very short.

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Competing interests: None of the authors has a relationship with any company that might have an interest in the submitted work, and none has any non-financial interests that may be relevant to the submitted work.
Ethical approval: Formal ethical review was not necessary for this study because only anonymised data were analyzed. The data file was created based on records of the Matlab Demographic Surveillance System (DSS) of ICDDR,B. DSS data collection and management procedures are approved by the ICDDR,B Ethical Review Committee.
Data sharing: No additional data are available. Permission of ICDDR,B may be sought to use Matlab DSS data for specific research questions.

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Table 1. Demographic characteristics of the sample, by IPI

IPI duration	Mother's age at miscarriage at beginning of IPI (s.d.)	Mother's age at outcome at end of IPI (s.d.)	MCH-FP Area (%)	Woman has no education (%)*	Gravida =2 (%)	Year 1977-1990 (%)	Year 1991-2000 (%)	Year 2001-2008 (%)	n
≤3 mos.	24.9 (5.8)	25.6 (5.8)	44.3	51.0	27.7	46.3	25.1	28.6	2,138
3-6 mos.	25.5 (6.1)	26.5 (6.0)	45.1	54.0	23.8	50.2	25.3	24.6	2,458
≤6 mos.	25.2 (6.0)	26.1 (6.0)	44.7	52.6	25.6	48.3	25.1	26.5	4,596
6-12 mos.	25.9 (6.4)	27.2 (6.4)	43.4	53.8	24.4	48.0	27.8	24.1	2,920
12-18 mos.	26.7 (6.7)	28.5 (6.7)	45.9	51.1	21.3	44.5	27.3	28.1	988
18-24 mos.	26.9 (6.8)	29.2 (6.7)	46.8	50.3	21.0	37.9	30.5	31.7	676
>24 mos.	27.0 (6.5)	31.5 (6.5)	46.7	50.0	17.4	29.9	34.3	35.8	1,255
24-36 mos.	27.4 (6.8)	30.5 (6.7)	46.6	50.3	17.4	33.2	32.3	34.5	579
36-48 mos.	27.0 (6.5)	31.1 (6.4)	48.6	45.9	18.8	33.2	29.8	37.0	292
>48 mos.	26.5 (6.0)	33.4 (6.0)	45.3	52.6	16.2	22.4	40.9	36.7	384
Total	25.9 (6.3)	27.5 (6.5)	44.8	52.4	23.5	45.0	27.6	27.4	10,435
Significance of differences across expanded IPI categories	P<0.001	P<0.001	ns	P=0.064	P<0.001	P<0.001	P<0.001	P<0.001	

ns = Not significant

* Among those with non-missing values. Education is not reported for 347 cases.

Table 2. Outcomes of subsequent pregnancy after miscarriage in previous pregnancy, by Interpregnancy Interval (IPI) (n=10,435)

	Outcome of Subsequent Pregnancy						
IPI duration	**Abortion**	**Miscarriage**	**Stillbirth**	**Live Birth**	**Total**	**Col. %**	
≤3 mos.	16	160	87	1,875	2,138	20.5	
(%)	(0.8)	(7.5)	(4.1)	(87.7)	(100.0)		
3-6 mos.	33	262	89	2,074	2,458	23.5	
(%)	(1.3)	(10.7)	(3.6)	(84.4)	(100.0)		
							Love et al. Col. %
≤6 mos.	49	422	176	3,949	4,596	44.0	41.2
(%)	(1.1)	(9.2)	(3.8)	(85.9)	(100.0)		
6-12 mos.	52	302	114	2,452	2,920	28.0	25.2
(%)	(1.8)	(10.3)	(3.9)	(84.0)	(100.0)		
12-18 mos.	25	125	45	793	988	9.5	9.6
(%)	(2.5)	(12.7)	(4.6)	(80.3)	(100.0)		
18-24 mos.	32	81	20	543	676	6.5	6.4
(%)	(4.7)	(12.0)	(3.0)	(80.3)	(100.0)		
>24 mos.	63	173	51	968	1,255	12.0	17.6
(%)	(5.0)	(13.8)	(4.1)	(77.1)	(100.0)		
Total	221	1,103	406	8,705	10,435	100.0	100.0
(%)	(2.1)	(10.6)	(3.9)	(83.4)	(100.0)		
% in Love et al.	(4.9)	(11.7)	(0.6)	(80.3)	(97.5)*		
24-36 mos.	15	66	29	469	578	5.5	
(%)	(2.6)	(11.4)	(5.0)	(81.1)	(100.0)		
36-48 mos.	19	38	9	226	290	2.8	
(%)	(6.5)	(13.1)	(3.1)	(77.9)	(100.0)		
>48	29	69	13	273	384	3.7	
(%)	(7.6)	(18.0)	(3.4)	(71.1)	100.0		

* The Love et al. numbers do not add to 100% because their data also included ectopic pregnancies (0.8% of all outcomes) and "other" outcomes (1.7% of all outcomes).

Table 3. Mortality outcomes after miscarriage in previous pregnancy, by Interpregnancy Interval (IPI) among all live births (n=8,705) (Mortality rates are calculated using denominator for infants alive and in Matlab at the beginning of the interval. [A total of 284 migrated out before age 1.])

	Child's age at death						
IPI duration	**First week**	**Week 2-4**	**Week 5-52**	**Known alive at 1 Year**	**Migrated out before Year 1**	**Total births**	**Col. %**
≤3 mos.	67	37	49	1,647	75	1,875	21.5
(%)	(3.6)	(2.0)	(2.6)	(87.8)	(4.0)	(100.0)	
3-6 mos.	64	26	54	1,868	62	2,074	23.8
(%)	(3.1)	(1.3)	(2.6)	(90.1)	(2.9)	(100.0)	
6-12 mos.	81	28	75	2,196	72	2,452	28.2
(%)	(3.3)	(1.1)	(3.1)	(89.6)	(2.9)	(100.0)	
12-18 mos.	31	8	13	714	27	793	9.1
(%)	(3.9)	(1.0)	(1.6)	(90.0)	(3.4)	(100.0)	
18-24 mos.	18	5	12	496	12	543	6.2
(%)	(3.3)	(0.9)	(2.2)	(91.3)	(2.2)	(100.0)	
24-36 mos.	16	2	7	438	16	469	5.4
(%)	(3.4)	(0.4)	(1.5)	(93.4)	(3.4)	(100.0)	
36-48 mos.	6	2	6	207	5	226	2.6
(%)	(2.7)	(0.8)	(2.7)	(91.5)	(2.2)	(100.0)	
>48	9	2	4	243	15	273	3.1
(%)	(3.3)	(0.7)	(1.5)	(89.0)	(5.5)	(100.0)	
Total	292	110	220	7,799	284	8,705	
(%)	(3.4)	(1.3)	(2.5)	(89.5)	(3.6)	100.0	
Rate per 1,000 at risk	33.5	13.1	26.6				

Figure 1. Relative risk ratios of induced abortion, miscarriage, and stillbirth following a miscarriage by IPI duration: unadjusted and adjusted results from Matlab and Love et al. (2010) (Note: Solid symbols indicate p <0.05)

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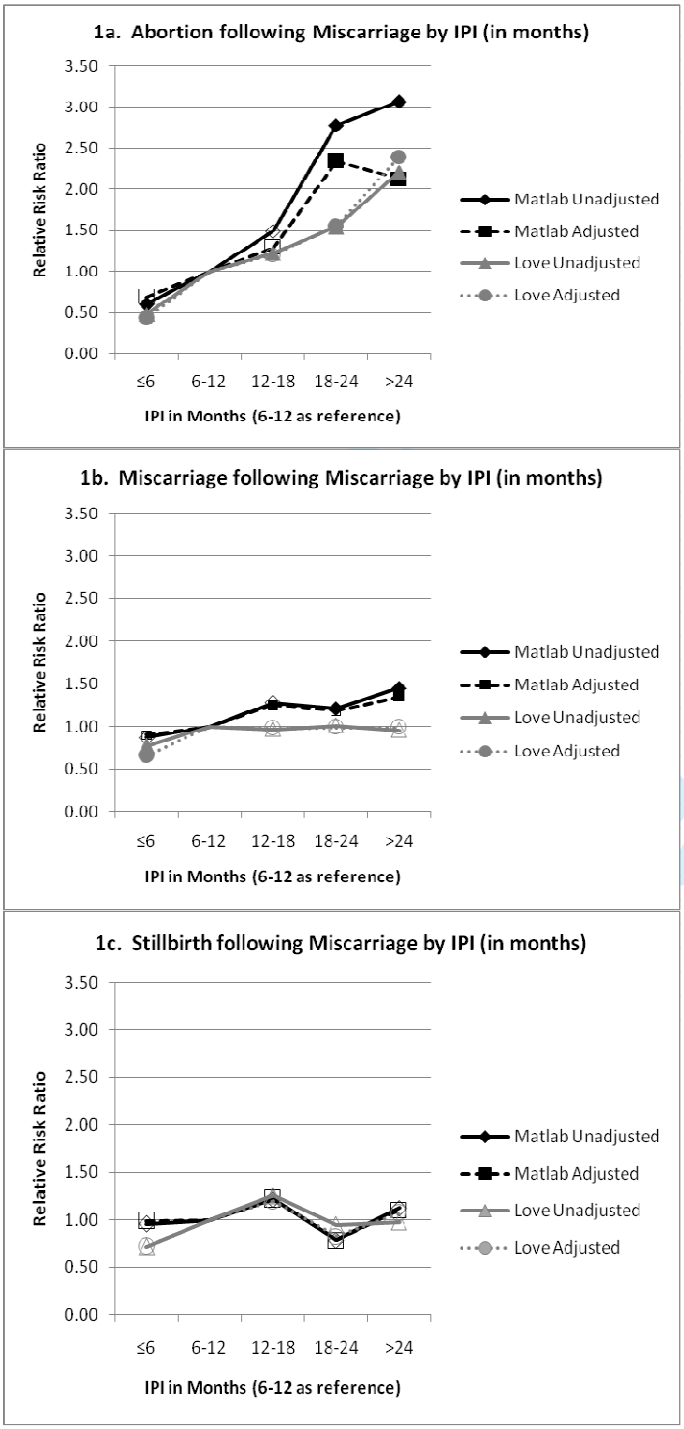

Figure 2. Relative risk ratios of induced abortion, miscarriage, and stillbirth following a miscarriage by expanded IPI categories: unadjusted and adjusted results for Matlab (Note: Solid symbols indicate p <0.05)

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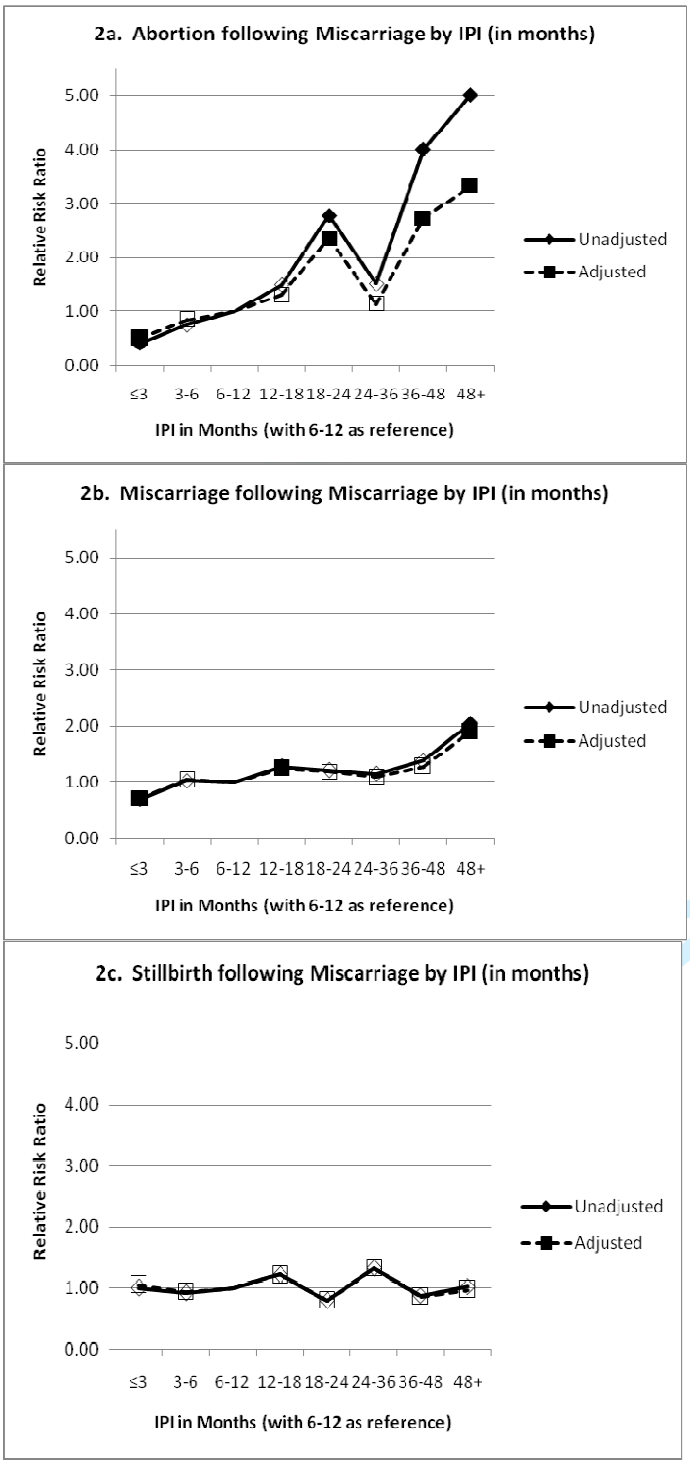

Figure 3. Hazard ratios of mortality during subperiods of infancy, by IPI duration, unadjusted and adjusted results from Matlab (Note: Solid symbols indicate p <0.05)

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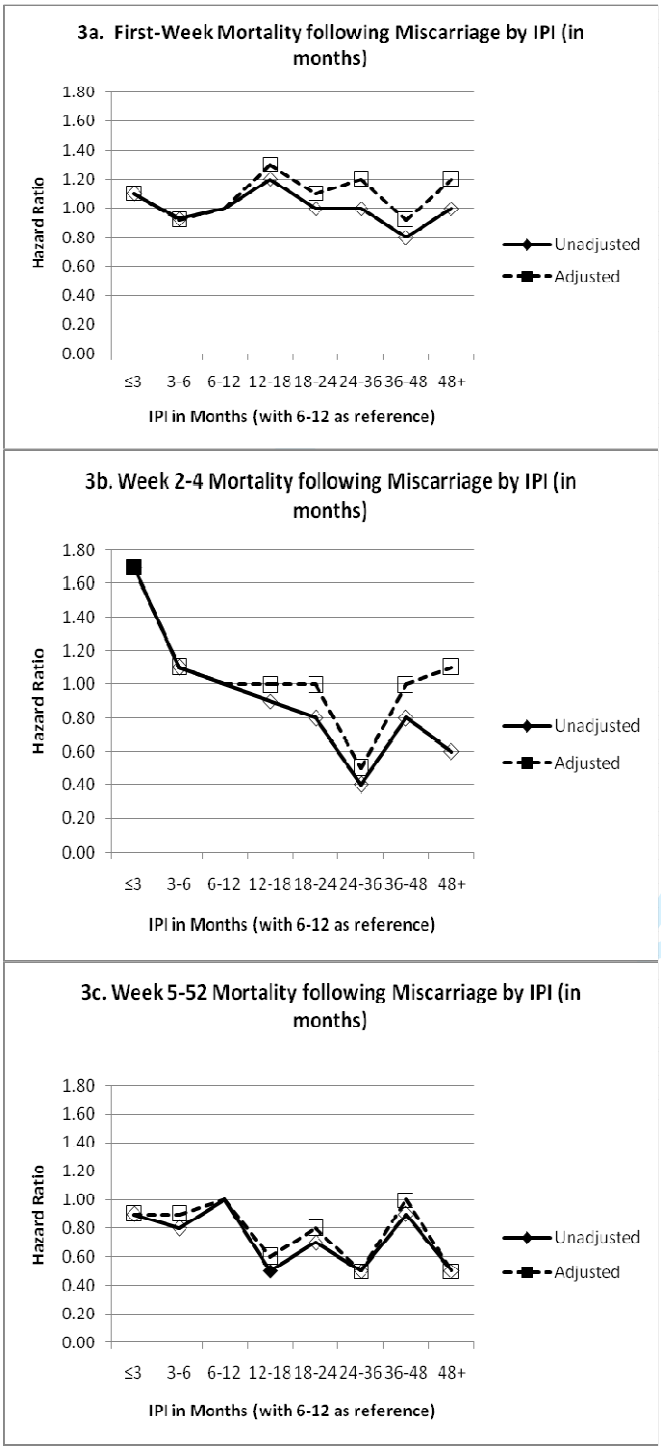

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We measure woman's age at the time of the focal outcome with a series of dichotomous indicators (age < 20, 20-24, 25-29, 30-34, 35-39, and 40+) to allow for non-linear effects. (The Love et al. article treats maternal age as a continuous variable and measures it at the time of the miscarriage that began the interval.) We measure SES by the woman's educational attainment. (We also considered the husband's education and housing size as additional measures of SES, but they never had statistically significant associations with pregnancy outcome. Love et al. use the Carstairs index as their measure of SES; such a measure is not available in our data.) We consider approximately 10-year bands of the calendar year of the focal outcome.

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(since we consider all pregnancies, whereas Love et al. considered only first pregnancies that ended in miscarriages)

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Of the women in our sample, 7,698 are represented once, and 1,516 have more than one observation (i.e., had more than one miscarriage that was followed by another pregnancy outcome). In order to adjust standard errors for the fact that we have more than one pregnancy for some women, w

	Item No.	Recommendation	Page(s) where addressed
Title and abstract			
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) *Cohort study*?Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*?Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls*Cross sectional study*?Give the eligibility criteria, and the sources and methods of selection of participants	4

		(*b*) *Cohort study*?For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*?For matched studies, give matching criteria and the number of controls per case	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	na
Study size	10	Explain how the study size was arrived at	4 (We consider all pregnancies documented in the DSS that began with a miscarriage in January 1977 or later and were followed by another pregnancy outcome not later than December 2008. We exclude from the sample focal pregnancies that ended with multiple live births.)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5

		(*c*) Explain how missing data were addressed	4-5
		(*d*) *Cohort study*?If applicable, explain how loss to follow-up was addressed *Case-control study*?If applicable, explain how matching of cases and controls was addressed*Cross sectional study*?If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	5-6, 8
Results			
Participants	13*	(*a*) Report numbers of individuals at each stage of study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	na
		(*b*) Give reasons for non-participation at each stage	na
		(*c*) Consider use of a flow diagram	na

Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(*b*) Indicate number of participants with missing data for each variable of interest	5 (re: missing information on date of last menstrual period) Table 1 (regarding missing information on the woman's education
		(*c*) *Cohort study*?Summarise follow-up time (eg average and total amount)	4
Outcome data	15*	*Cohort study*?Report numbers of outcome events or summary measures over time	Table 2
		*Case-control study?*Report numbers in each exposure category, or summary measures of exposure	na
		*Cross sectional study?*Report numbers of outcome events or summary measures	na
Main results	16	(*a*) Report the numbers of individuals at each stage of the study?eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(*b*) Give reasons for non-participation at each stage	4
		(*c*) Consider use of a flow diagram	na

Other analyses	17	Report other analyses done?eg analyses of subgroups and interactions, and sensitivity analyses	5
Discussion			
Key results	18	Summarise key results with reference to study objectives	6-7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

How Long After a Miscarriage Should Women Wait Before Becoming Pregnant Again?~~The Effects of Pregnancy Spacing After a Miscarriage on Subsequent Pregnancy Outcomes: Evidence~~ Multivariate Analysis of Cohort Data from Matlab, Bangladesh

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ABSTRACT

Objective To determine the optimum interpregnancy interval (IPI) following a miscarriage ~~and to see if findings for a poor, rural area in Bangladesh are similar to those in a recent study of Scottish women~~.

Design Observational population-based study~~Multivariate analysis of population-based, prospective data from a demographic surveillance system (study cohort)~~.

Setting Pregnancies in Matlab, Bangladesh, between 1977 and 2008.

Participants 9,214 women with 10,453 pregnancies that ended in a miscarriage and were followed by another pregnancy outcome.

Main outcome measures Outcome of pregnancy following the miscarriage was singleton live birth, stillbirth, miscarriage, or induced abortion. For pregnancies that ended in live birth: early neonatal, late neonatal, and post-neonatal mortality~~, whether the child died in first week of life, in the next three weeks, or between 29 days and one year of age~~.

Results Compared with interpregnancy intervals (IPIs) of 6-12 months, pregnancies that were conceived ≤3~~less than three~~ months after a miscarriage were more likely to result in a live birth and less likely to result in a miscarriage (adjusted odds ratio 0.70, 95% confidence interval 0.57 to 0.86) or induced abortion (0.50, 0.29 to 0.89). Induced abortions were significantly more likely following IPIs of 18-24 months (2.36, 1.48 to 3.76), 36-48 months (2.73, 1.50 to 4.94), and ≥~~more than~~ 48 months (3.32, 1.68 to 2.95), and miscarriages were more likely following IPIs of 12-17 months (1.25, 1.01 to 1.56) and ≥~~more than~~ 48 months (1.90, 1.40 to 2.58). No significant effects of IPI duration are seen on the risks of a stillbirth. ~~These results are remarkably similar to those in a recent analysis of a large sample of Scottish women.~~ However, ~~we find a different pattern when we consider whether the infant born at the end of the IPI died: Compared to IPIs of 6-12 months, the shortest~~ IPIs ≤3 months following a miscarriage ~~(≤3 months)~~ are associated with significantly higher late neonatal mortality for the infant born at the end of the IPI (adjusted relative risk ratio 1.74, 1.06 to 2.84), and IPIs of 12-18 months are associated with a significantly lower unadjusted risk of post-neonatal mortality (0.54, 0.30 to 0.96).

Conclusions The shorter the IPI following a miscarriage, the more likely the subsequent pregnancy is to result in a live birth. However, very short IPIs may not be advisable in poor countries like Bangladesh because they are associated with a higher risk of mortality for the infants born after them.

ARTICLE SUMMARY

Article Focus

- To assess the associate between the duration of the interpregnancy interval (IPI) following a miscarriage and the outcome of the next pregnancy in Matlab, Bangladesh

Key Messages

- The shorter the IPI following a miscarriage, the more likely the subsequent pregnancy is to result in a live birth.
- However, very short IPIs (≤3 months) are associated with a higher risk of mortality for the infants born after them.
- Hence, very short IPIs may not be advisable in poor countries like Bangladesh.

Strengths and Limitations of this Study

- Study considers data from a poor developing area – rural Bangladesh. Most previous studies of this topic have been of industrialized countries.

- Sample size (10,453) is larger than that in most studies of this topic, though not as large as in a recent study of Scottish women.
- Study considers mortality during infancy in addition to pregnancy outcomes.
- Study considers effects of even shorter and even longer intervals than previously considered.
- Data on pregnancy outcomes were carefully collected and likely to be of high quality, but probably not as high quality as clinical data.

~~**WHAT IS ALREADY KNOWN ABOUT THIS TOPIC**~~

~~Most previous studies of the effects of pregnancy spacing have considered intervals following live births~~

~~A recent study of Scottish women finds that after an initial miscarriage, women had the best pregnancy outcomes if they conceived again within six months and the worst outcomes if they didn't conceive until at least 24 months after the miscarriage~~

~~It is not known whether this is also true for women in poor, developing countries or whether the duration of the IPI following a miscarriage affects infant mortality~~

~~**WHAT THIS STUDY ADDS**~~

~~As was found in the study of Scottish women, after a miscarriage Bangladeshi women were most likely to have a live birth (compared to another type of pregnancy outcome) if they conceived again within six months and least likely if they did not conceive until at least 24 months after the miscarriage~~

~~In Bangladesh, pregnancy outcomes after a miscarriage were best for even shorter intervals (≤3 months) than considered in the Scottish study and worst for even longer intervals (>48 months)~~

~~However, patterns are different for infant survival outcomes: Compared to intervals of 6-12 months, the shortest intervals following a miscarriage (≤3 months) are associated with significantly higher unadjusted and adjusted risks of late neonatal mortality, and intervals of 12-18 months are associated with a significantly lower unadjusted risk of post-neonatal mortality~~

INTRODUCTION

Many studies have assddressed the effect on maternal[1] and perinatal[2] outcomes and on infant and child mortality[3] of pregnancy spacing following a live birth or following a live birth or stillbirth. However, very few studies have sought to identify the optimum interpregnancy interval (IPI) following a miscarriage (spontaneous abortion); the studies that have been done are generally of women living in industrialized countries, and most have relatively small sample sizes.[4 5 6] A~~n article by Love et al. published in this journal in 2010~~ recent study[7] that considered a large sample of women who delivered in Scottish hospitals ~~to look at the effects of IPIs that began with a miscarriage. The study~~ found that women who conceived within six months after a miscarriage had better outcomes of the subsequent pregnancy than women who waited longer to conceive again; e.g., they were less likely to have a voluntary pregnancy termination (induced abortion) or another miscarriage. In this paper we investigate whether these same findings are seen in a very different setting – among poor women in rural Bangladesh. We also investigate whether infants born at the ends of the intervals died before their first birthday. Women in Bangladesh are more likely to be malnourished than those in industrialized countries,[8] and hence may be more likely to be nutritionally depleted by a pregnancy, even one that ends in miscarriage.

METHODS

We use high-quality longitudinal data from the Matlab Demographic Surveillance System (DSS). Matlab is a rural sub-district of Bangladesh that is well known for its DSS and its Maternal Child Heath-Family Planning (MCH-FP) project, which operates in half of the area covered by the DSS to provide intensive and quality family planning and maternal/child health services.[9 10 11] ~~The other half, known as Comparison Area, is typical of much of Bangladesh in contraceptive use,[12] fertility and childhood mortality,[13] and maternal mortality.[14] The MCH-FP Area has lower fertility rates[15] and lower rates of induced abortion,[16] miscarriage,[17] and stillbirth,[18] and greater coverage of antenatal care and better access to basic and emergency obstetric care than the Comparison Area.[15 18]~~

The Matlab DSS contains, for both areas of Matlab, longitudinal records of pregnancy outcomes and deaths for all household members. During their regular visits to each household, fortnightly between 1966 and 1999, monthly between 2000 and 2006, and bimonthly since 2007, the community health workers (CHWs) record pregnancy status at the time of the visit and any pregnancy outcomes or household deaths that occurred prior to the visit.

~~The DSS provides information on 245,091 pregnancies that occurred between 1974 and 2008. In t~~This study ~~we~~ considers the 10,435 pregnancies documented in the DSS that began with a miscarriage in January 1977 or later and were followed by another pregnancy outcome (here called the "focal pregnancy") other than a multiple live birth not later than December 2008. Before 1977, the DSS did not distinguish between spontaneous and induced abortions. In the DSS, a *miscarriage* (spontaneous abortion) is defined as a spontaneous fetal loss prior to 28 weeks gestation. We exclude from the sample 246 focal pregnancies that ended with multiple live births~~; 246 pregnancies are excluded for this reason~~.

We consider the following outcomes of the focal pregnancies that follow the IPI after a miscarriage: singleton live birth, stillbirth, miscarriage, and induced abortion. In the DSS, a *live birth* is the delivery of a live baby at any gestational age; a *stillbirth* is a fetal loss at 28 weeks or longer gestation; ~~as noted above, a spontaneous abortion, or *miscarriage*, is a spontaneous fetal loss prior to 28 weeks;~~ and *induced abortion* is self-reported. Early-gestation pregnancy termination is legal in Bangladesh if performed in a medical setting before the pregnancy is clinically confirmed. Such pregnancy terminations are done by manual vacuum aspiration by trained female paramedics at the government Health and Family Welfare Centers and are known as "menstrual regulation~~,~~" ~~or "~~(MR~~)~~.~~"~~ MR can be performed ~~only~~ within ~~10~~ 8 weeks of the last menstrual period before pregnancy is clinically confirmed. MR has been available through government and other medical facilities in Bangladesh since the late 1970s, when the government

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agreed to permit such pregnancy terminations in an effort to replace the practice of unsafe abortion. Pregnancy termination in a non-medical setting or after pregnancy is clinically confirmed is prohibited in Bangladesh except when done to save a woman's life. Our "induced abortion" category includes both MRs and voluntary pregnancy terminations by other means. (~~Method~~ Since 1989, when method of pregnancy termination ~~has been~~was first distinguished in the DSS ~~since 1989. Since then~~, 52% of terminations have been by MR, 3% by D&C, and 45% by other means.)

We also consider mortality of the children born in the focal pregnancies during three subperiods of the ~~child's~~ first year of life – early neonatal (first week of life), late neonatal (next three weeks of life), and post-neonatal (the rest of the first year of life). The sample for our analyses of early neonatal mortality is the 8,705 ~~pregnancy intervals~~IPIs that began with a miscarriage and ended with a live birth. The sample for late neonatal mortality is the 8,401 of these that survived the first week of life and were still living in Matlab, and the sample for post-neonatal mortality is the 8,268 of these that survived the first four weeks of life and were still living in Matlab.

The duration of the IPI is defined by measuring the amount of time between the preceding miscarriage and the estimated date of conception of the focal pregnancy. For the 5,914 cases for which we know the date of the last menstrual period (DLMP), we estimate the date of conception as occurring two weeks after the DLMP before the focal pregnancy. For the 4,519 cases for which DLMP was not reported, we estimate the duration of the IPI as the amount of time between the miscarriage and the end of the focal pregnancy less the estimated duration of the focal pregnancy, based on the outcome of that focal pregnancy. Our estimate of duration of each type of pregnancy outcome is the average duration of all pregnancies that ended with that outcome for which we know DLMP. These averages are 36 weeks for live births, 33 weeks for stillbirths, 11 weeks for miscarriages, and 8 weeks for induced abortions. We have also done all analyses only for the cases for which DLMP was reported; ~~, and~~ the sizes of the odds ratios and relative risks are similar to those reported here.

Our multivariate analyses control for the woman's age at the time of the focal outcome (with ~~a series of~~ dichotomous indicators for ~~{~~age < 20, 20-24, 25-29, 30-34, 35-39, and ≥40~~+)}~~ ~~to allow for non-linear effects)~~, ~~a proxy for socioeconomic status (~~the woman's educational attainment~~)~~, and calendar year (approximately 10-year bands of the calendar year of the focal outcome). (We used interactions to explore whether the IPI effects varied over time, but these were never statistically significant.) We also control for the gravidity of the focal pregnancy (dichotomous indicators) and for whether the woman lived in the MCH-FP Area or the Comparison Area of Matlab. Data on maternal age, gravidity, area, and calendar year all come from the DSS. Information on women's education is from periodic censuses conducted by ~~ICDDR,B~~icddr,b in the Matlab area. Most of the potential confounders vary significantly with IPI, as can be seen in Table 1. Women's ages at both the beginnings and ends of the IPI are positively related to IPI duration, and longer IPIs are more likely to be for higher gravidity and to occur in the later years covered by the data.

Statistical analysis

We assess the effects of the duration of the IPI on the outcome of the subsequent pregnancy with ~~crude~~ unadjusted and adjusted odds ratios that derive from univariate and multivariate multinomial logistic regressions. The effects of IPI duration on mortality during subperiods of infancy are estimated with Cox proportional hazards models. All models are estimated by Stata 11.0. The hazard model allows for censoring due to moving out of the Matlab area or not completing the at-risk period by the end of 2008. The multivariate analyses control for the variables mentioned above. We used the cluster command in Stata 11.0 to adjust standard errors for the fact that ~~we have more than one pregnancy for~~ 1,516 ~~some~~ women have more than one pregnancy in the sample~~. Of the women in our sample, 7,698 are represented once, and 1,516~~

~~have more than one observation (i.e., had more than one miscarriage that was followed by another pregnancy outcome)~~.

To facilitate comparisons we consider the same categories of IPI durations considered by the recent Love et al. study of Scottish women -- ≤6 months (0 to 24 weeks), 6-12, months (25-52 weeks) (reference category), 12-18 months (53 -76 weeks), 18-24 months (77-104 weeks), and >24 months (105 or more weeks), where each category includes the upper bound but not the lower bound. We also conduct analyses that consider additional categories of IPIs, breaking the ≤6 months category into ≤3 months (0-12 weeks) and 4-6 months (13 -24 weeks) to assess the effects of very short intervals, and breaking the >24 months category into 24-36 months, 36-48 months, and >48 months, since other studies have found different effects of such longer intervals.[19]

RESULTS

The middle of Table 2 shows the cross-tabulation of IPI duration and outcome of the focal pregnancy for the IPI categories considered by Love et al. The rows above that show the finer breakdown of the ≤6 months category, and the rows below that show the finer breakdown of the >24 months category. Of the 10,435 cases in our sample, 4,596 (44.0%) conceived ≤6 months ~~or less~~ after the miscarriage (20.5% ~~≤within~~ 3 months ~~or less~~ and 23.5% in 4-6 months). The next largest percentage is for IPIs of 6-12 months (28.0%). The percentages for IPIs of 12-18 and 18-24 months are 9.5% and 6.5%, respectively. IPIs ~~>longer than~~ 24 months comprise 12.0% of the sample (5.5% are 24-36 months long, 2.8% are 36-48 months, and 3.7% are ~~>longer than~~ 48 months). We find a somewhat higher incidence of short intervals (~~≤of~~ 12 months ~~or less~~) and a somewhat lower incidence of long intervals (~~>more than~~ 24 months) than Love et al. find for Scottish women, but, as seen in the right-hand column of Table 2, the IPI distributions are ~~generally fairly~~quite similar~~, as can be seen in the right-hand column of Table 2~~.

Of all IPIs that began with a miscarriage, 2.1% ended with an induced abortion, 10.6% ended with another miscarriage, 3.9% ended with a stillbirth, and 83.4% ended with a live birth (Table 2). The percentage of post-miscarriage pregnancies that end with a live birth decreases as the length of the IPI increases. It is highest for the shortest IPIs (85.9% for IPI ≤6 months and 87.7% for IPI ≤3 months) and lowest for the longest IPIs (77.1% for IPI >24 months and 71.1% for IPI >48 months). The percentages for induced abortion and miscarriage each increase nearly monotonically as IPI increases, but there is little systematic pattern for stillbirths. A similar pattern was found for Scottish women, as can be seen in Table 2, though the incidence of stillbirth is lower in their data and the incidence of induced abortion higher than we find for Matlab, Bangladesh.

Of all IPIs that began with a miscarriage and ended with a live birth, 292 of those live-born children died in their first week of life (33.5 early neonatal deaths per 1,000 live births). Of those who survived the first week, 13.1/1,000 died in the next three weeks. And of those who survived the first four weeks, 26.6/1,000 died before their first birthday (Table 3). The patterns of how mortality varies with duration of IPI are not as smooth as those for pregnancy outcomes, but they show that the risks of mortality are often higher for the shorter IPIs and lower for the longer IPIs. The percentage of babies known to be alive at one year is below the sample average for IPI ≤3 months and above the sample average for ~~all IPI categories of longer than~~ 3 months <IPI ~~and ≤less than~~ 36 months.

~~Figure 1 shows~~ The patterns of how the unadjusted and adjusted odds ratios of the outcome of the focal pregnancy vary with IPI duration are quite similar in our data and ~~how they compare to those found by~~in the Love et al. data ~~for~~ on Scottish women (Figure 1). ~~The patterns are quite similar in the two studies.~~ In both studies, no significant effects of IPI duration are seen on the risks of a stillbirth, but the unadjusted odds of induced abortion increase monotonically as IPI duration increases, being lowest for ~~IPIs of less than~~ IPI ≤6 months (for Matlab unadjusted OR for IPI ≤6 months = 0.59, 95% confidence interval 0.40 to 0.86, relative to IPI=6-12 months)

and highest for IPIs of ~~at least~~≥24 months (for Matlab unadjusted OR= 3.07 [2.11 to 4.46] relative to IPI=6-12 months). In Matlab, the unadjusted odds of a subsequent miscarriage also generally increase with IPI duration, being highest for IPIs of ~~at least~~≥24 months, whereas in Scotland long IPIs we~~a~~re not associated with higher odds of miscarriage. For both induced abortion and miscarriage, the patterns are very similar in the two studies for the shortest IPIs, but the pernicious effects of long intervals on the unadjusted odds are larger for Matlab than in Scotland. Adjusting for other variables generally has more effect in our data from Matlab than it did in ~~Love et al.'s~~the Scottish data ~~from Scotland~~. In the Matlab data, the effect of adjustment is greatest for the longest intervals, so much so that the adjusted odds ratio for IPIs ~~of at least~~≥24 months on induced abortion is slightly lower for Matlab than for Scotland.

~~Figure 2 show~~Us ~~u~~nadjusted and adjusted odds ratios of the focal-pregnancy outcome ~~of the focal pregnancy~~ for our finer breakdown of IPI categories~~. It show~~s that the same patterns persist *within* the IPI ≤6 months and IPI >24 months categories (Figure 2), though the odds of a live birth for 24-36 months are lower than those for 18-24 months. Relative to IPI=6-12 months p~~P~~regnancies that were conceived ≤3~~less than three~~ months after a miscarriage were the most likely to result in a live birth and least likely to result in a miscarriage (adjusted odds ratio 0.70, 95% confidence interval 0.59 to 0.86~~, relative to IPI=6-12 months~~) or induced abortion (0.50, 0.29 to 0.89). Induced abortions were more likely following IPIs of 18-24 months (2.36, 1.48 to 3.75), 36-48 months (2.73, 1.50 to 4.94), ~~and more than~~ ≥48 months (3.32, 2.05 to 5.38); and miscarriages were more likely following IPIs of 12-17 months (1.25, 1.01 to 1.56) and ~~more than~~≥48 months (1.90, 1.40 to 2.58)**.** Again, adjustment has a greater effect the longer the IPI. Again, no significant effects of IPI duration are seen on the risks of a stillbirth.

Figure 3 shows the hazard ratios of mortality during the three subperiods of infancy for our finer breakdown of IPI categories. We find no significant relationships between IPI duration and early neonatal mortality in ~~either~~ our unadjusted or adjusted analyses. However, for late neonatal mortality, in both the unadjusted and the adjusted analyses, we find significantly higher risk of mortality for IPIs ≤3 months (adjusted relative risk ratio 1.74, 1.06 to 2.84) and generally see a decline in mortality as IPI duration increases up to 36 months. We find a significantly lower unadjusted risk of post-neonatal mortality ~~(between the 5th and 52nd week of life)~~ for IPIs of 12-18 months compared to those of 6-12 months (0.54, 0.30 to 0.96). (The adjusted risk ratio is similar but is not statistically significant [0.56, 0.31 to 1.01].)

DISCUSSION

We find that the shorter IPI following a miscarriage, the more likely the subsequent pregnancy is to result in a live birth. Women with IPIs of ~~at least~~≥18 months following a miscarriage, and especially those with intervals of ~~at least~~≥48 months have a much higher likelihood of experiencing another miscarriage or having an induced abortion. The odds of an induced abortion following a miscarriage are particularly high for the longest IPI category (unadjusted OR for IPI>48 months = 5.02 [3.13 to 8.03] and adjusted OR = 3.32 [2.05 to 5.38]). Adjusting for the effects of demographic and socioeconomic variables reduces the effect of long intervals on induced abortion, but they remain large and significant. No significant effects of IPI duration are seen on the risks of a stillbirth.

However, we see quite different patterns when we consider the effect of pregnancy spacing after a miscarriage on ~~early and~~ late neonatal and post-neonatal mortality. Compared to IPIs of 6-12 months, the shortest IPIs following a miscarriage (≤3 months) are associated with significantly higher unadjusted and adjusted risks of late neonatal mortality, and IPIs of 12-18 months are associated with a significantly lower unadjusted risk of post-neonatal mortality. ~~Hence, we find some evidence that short IPIs are associated with higher mortality between the first week and the end of the first year of life for the children born after a miscarriage.~~ It appears that children born after very short IPIs following a miscarriage are able to survive the first week of life but then are at higher risk of dying in the rest of the first year.

Comparison to other studies

Most studies of the effects of pregnancy spacing consider intervals that began with a live birth or with a live birth or stillbirth.[1-3 20] They generally find adverse effects of both short and long intervals, but the "optimum" interval (the one with the lowest risk of an adverse outcome) differs across types of outcomes. For example, a study of the U.S. that considers intervals that began with live births finds the lowest risks of adverse perinatal outcomes for IPIs of 18-23 months duration.[21] A meta-analysis of the effects of intervals following live births on perinatal outcomes found that intervals of 18-59 months are associated with better outcomes than shorter and longer intervals,[2] and a review of studies of maternal outcomes reaches a similar conclusion.[1] An analysis of data from a number of developing countries found infant mortality to be lowest for intervals of ~~at least~~≥~~-~~24 months duration that began with live births, and under-five mortality to be lowest for intervals of ~~at least~~≥~~-~~36 months.[3]

A study of the Matlab MCH-FP Area found that following live births the risks of miscarriage and of stillbirth in the next pregnancy were significantly higher for IPIs ~~shorter than~~≤ 6 months (compared to those of 27-50 months duration).[19] That study did not distinguish the type of outcome that began IPIs longer than 50 months~~, but most of such longer IPIs began with a live birth and the likelihoods of miscarriage and of stillbirth were also significantly higher for IPIs of 75 months or longer compared to those of 27-50 months that began with a live birth~~. ~~Two~~ An earlier ~~-~~study~~ies~~ in Bangladesh ~~, however,~~ found ~~no relationship between late~~a higher risk of early fetal death (~~after 28 weeks of gestation~~first or second trimester) ~~and~~ following short IPIs (<12 months) ~~compared with intervals longer than 24 months~~that began with the birth of a surviving child who breastfed.[22 23] Studies using data from Sweden found that very short (~~0~~ ≤3 months) IPIs following live births were associated with higher risks of stillbirth.[24 25] Studies of World Fertility Survey data from a number of developing countries found IPIs ~~of less than~~<~~-~~9 months following live births to be associated with higher risks of fetal death;[26 27] early fetal losses and stillbirths were combined in those studies.

~~We consider intervals that began with a miscarriage, in essence asking the question "How long after a miscarriage should a woman wait before becoming pregnant again?" There are~~ V~~v~~ery few studies have ~~that~~ looked specifically at IPIs that began with a miscarriage, as we do here.

A study of Latin America that assessed the effects of intervals following induced and spontaneous abortions found that intervals ~~shorter than six~~<6 months between abortion and subsequent pregnancy were associated with elevated risks of premature rupturing of membranes, anemia and bleeding, pre-term and very pre-term births, and low birthweight, compared with longer intervals.[28] However, that study ~~was~~ did not ~~able to~~ distinguish between induced and spontaneous abortions. 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 mores~~t~~ likely to have been intended. Based on the study of Latin America just mentioned, WHO currently recommends "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."[29] ~~This recommendation is based on the study of Latin America just mentioned.[28]~~ ~~-~~The report on the WHO Technical Consultation that makes that recommendation ~~also~~ recommends "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).[29]

Three studies[4-6] using data from the U.S. or Europe find no effects of the duration of IPI following a miscarriage on the outcome of the subsequent pregnancy, but their samples are relatively small (64, 91, and 1,530 respectively). An earlier study of Matlab that considered a much smaller sample of IPIs that began with a miscarriage than that considered here and only in the MCH-FP Area also found, ~~like~~ as we do here, a decreasing likelihood of having a live birth

following a miscarriage as duration of the preceding IPI increases.[19] However, that study did not consider longer intervals that began with a miscarriage.

Love et al.'s recent study uses a large sample of pregnancies to Scottish women who had a miscarriage to assess the effects of pregnancy spacing ~~of~~ on the outcome of the subsequent pregnancy.[7] We have constructed our analyses to be as similar as possible to those of Love et al., to facilitate comparisons. Our results for pregnancy outcomes are remarkably similar to theirs. Both studies find that short IPIs following a miscarriage are associated with lower risks of a subsequent miscarriage or an induced abortion, and long intervals are associated with higher risks of these outcomes, and both find no significant effects of the duration of the post-miscarriage IPI ~~following a miscarriage~~ on the risk of stillbirth.

We also examine even shorter and longer IPIs durations than Love et al. do and show that the very shortest intervals we consider (≤~~-~~3 months) are associated with the lowest risks of induced abortion and miscarriage and the longest (>48 months) are associated with the highest risks of these outcomes. ~~For example, for the likelihood of another miscarriage, we do not see the significant "beneficial" effect of IPI ≤6 months (relative to IPI = 6-12 months) found by Love et al., but we do see a beneficial effect when we consider IPI ≤3 months (adjusted odds ratio 0.70, 95% confidence interval 0.57 to 0.86).~~

We generally find even stronger pernicious effects of long intervals on the odds of a miscarriage or an induced abortion in the focal pregnancy than was found for Scottish women, and the effects are particularly large when we consider an expanded set of IPI categories (up to >48 months). Adjusting for the effects of demographic and socioeconomic variables reduces the effects of long intervals on the likelihood of induced abortion more for Matlab than it did in Love et al.'s study of Scotland; the adjusted risk associated with intervals of ~~more than~~ ≥24 months (compared to those of 6-12 months) is slightly lower for Matlab than those Love et al. found for Scotland (whereas the opposite is true for unadjusted risks). 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 subsample and found patterns similar to those reported here, but they were not statistically significant.

We find some evidence that short IPIs following miscarriages are associated with higher mortality between the first week and the end of the first year of life for the children born after a miscarriage. Another study of Matlab found that short inter-outcome intervals (~~less than~~≤~~-~~15 months between one pregnancy outcome and the next outcome) that began with a miscarriage were associated with higher risks of early and late neonatal mortality compared with intervals of 36-59 months that began with the live birth of a child who survived.[30] (However, that study did not compare them to longer ~~inter-outcome~~ intervals that began with a miscarriage.) By contrast Love et al. do not find short IPIs to be associated with higher risks of preterm delivery and low birthweight – outcomes that have been widely found to be associated with mortality during infancy.[31 32] The better nutritional status of Scottish women may buffer their fetuses from the depleting effects of a recent previous miscarriage.

Previous studies have offered a number of hypotheses to explain ~~the effects of IPIs on maternal, perinatal, and infant and child health outcomes. The main hypotheses offered to explain~~ why there might be adverse effects of short IPIs, the main ones being ~~are~~ (1) competition for family resources and time from a just-older sibling;[30] (2) transmission of infection among closely-spaced siblings~~-~~;[30] and (3) maternal depletion,[33] especially of folate.[34] The first and second mechanisms would only come into play for intervals that began with live births of children who survived, and ~~clearly~~ hence do not apply to ~~our case of~~ IPIs that began with miscarriages. Maternal depletion is more likely the longer the pregnancy ~~(and, if the pregnancy results in the live birth of a child who survives, breastfeeding, especially if unsupplemented, can~~

~~further deplete the woman)~~.[33] Folate depletion begins around 5 months gestation.[34] Since our definition of miscarriages includes pregnancies up to 28 weeks gestation, some of the pregnancies could lead to folate depletion. 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.[35]

Our finding that short IPIs following a miscarriage are associated with a ~~higher~~ greater likelihood of a live birth at the end of the interval is consistent with the notion that most women who had a miscarriage wanted to have a live birth, and as a result many of them seek to become pregnant again as soon as possible and may take very good care of themselves during the subsequent pregnancy. A fifth (20.5%) of the women in our sample who experienced a miscarriage and became pregnant again did so within three months of the miscarriage, and ~~nearly half (~~44.0%~~)~~ were pregnant within six months.

To explain the adverse effects of long IPIs on pregnancy outcomes, it has 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,[21] which have been shown to have higher risk of many poor outcomes.[36] It is also possible that long intervals are selective of women in poorer health, who take longer to conceive,[37] or that women who have long intervals did not want to become pregnant again and do not take as good care of themselves during pregnancy.[19] In addition, long IPIs are more likely for older women; older maternal age is associated with its own independent adverse effects on pregnancy outcomes,[38] though we see an effect even when we control for maternal age. A meta-analysis has shown that IPIs longer than 59 months are associated with adverse perinatal outcomes.[19] That study also found adverse effects on perinatal outcomes of intervals shorter than 18 months, which we do not see for pregnancy outcomes, but we do see some adverse effects of very short intervals on infant survival. Other studies of Matlab have shown that women with long intervals (but not distinguishing the type of outcome with which they began) have higher risks of pregnancy complications,[39] maternal mortality,[37] and induced abortion.[19]

Strengths and weaknesses of the study

We look at the effects of IPIs following miscarriages, allowing conclusions about how long women should wait after a miscarriage before becoming pregnant again. We replicate the Love et al. study,[7] which also looked at this question, in a very different setting – poor women in rural Bangladesh. Furthermore, we examine the effects of shorter and longer intervals than considered by Love et al. We consider recent data (up to 2008) -- more recent than ~~those~~ considered by~~in the~~ Love et al. ~~study (which covered the period~~ 1981-2000).

The Matlab DSS data on induced ~~and spontaneous~~ abortion -and ~~(~~miscarriage~~)~~ are likely to be of high quality and not to suffer from underreporting. In their many years of work in the community the CHWs have established themselves as trustworthy and in a good position to collect reliable information on pregnancy outcomes and, because of their frequent household visits, they are likely to elicit accurate information.[9] Nonetheless, there is probably an under-reporting of early miscarriages since these may not have been identified as pregnancies, and there may be some underreporting of ~~voluntary pregnancy terminations~~induced abortions and some misreporting of ~~such terminations~~these as miscarriages. Furthermore, the gestation of pregnancy is based on women's reports of the date of their last menstrual period (DLMP), rather than on sonography, which is very rare in Matlab. The reports of DLMP, however, are likely to be quite accurate, since the respondents were visited regularly and the recall periods were relatively short.

The DSS defines a stillbirth as a fetal loss at 28 weeks or longer gestation and ~~spontaneous abortion, or~~ miscarriage ~~,~~ ~~a~~is a spontaneous fetal loss prior to 28 weeks. Some studies define stillbirth starting at 20~~+~~ weeks (and Love et al. use a 24-week cutoff), so their definition of stillbirth overlaps with our definition of miscarriage. In our data, for cases for which we know DLMP, there were 50 (of 578) cases where the focal outcome was coded as a miscarriage and the duration of gestation was 20-27 weeks. We are not able to recode these cases, however, because we do not know pregnancy duration for cases for which DLMP is not reported and must rely on the reported outcome of pregnancy 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+- or 24+-week definition.

Though smaller than the sample used by Love et al, our sample (n=10,435) is much larger than that used in other studies of this topic.[4-6 19]

~~We consider effects of IPI after a miscarriage on pregnancy outcomes – live birth, stillbirth, miscarriage, and induced abortion – but we are not able to look at ectopic pregnancies as~~ Love et al. ~~do. They~~ found a positive association of the duration of the IPI with the incidence of ectopic pregnancy, ~~and also with~~ caesarean section, preterm delivery, and low birth weight. We either do not have these indicators in our data or have them only for a subsample too small to permit analyses. However, unlike Love et al., for IPIs that end in live births, we look at the mortality of those children during three subperiods of infancy.

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.

Implications for research

This study is of a setting, ~~in~~ rural Bangladesh, ~~with~~ where fertility and infant mortality rates ~~that~~ are relatively high but have fallen considerably over the study period, and one half of the area studied has been exposed to more intense, higher-quality family planning services than are available in many developing countries. The study should be replicated in other settings. Future studies should adjust for the effects of ~~additional~~ potentially confounding variables ~~(such as those mentioned above)~~ and ~~should~~ assess the effects of the durations of IPIs following miscarriages on the health and survival of the children born at the end of those intervals as well as on those of their mothers. Studies should also assess the effects of IPIs that began with stillbirths and of IPIs that began with induced abortions~~, and they should investigate the influence of the duration of pregnancy gestation at the time of the fetal loss~~.

Implications for clinical practice

The current WHO recommendation is that women should wait at least six months after a miscarriage or induced abortion before becoming pregnant again. However, as noted above, that recommendation was based on one study of Latin America of the effects of IPIs following induced *or* spontaneous abortions.[28] Our study, of Matlab, Bangladesh, like that of Love et al. for Scotland,[7] other studies of industrialized countries,[4-6] and a smaller study of Matlab,[19] looks specifically at the effects of IPIs following miscarriages~~, and~~; all of the studies find no higher risk of adverse pregnancy outcomes if women become pregnant soon after a miscarriage. However, we find that very short intervals (≤~~-~~3 months) following a miscarriage are associated with higher mortality risks for infants in Bangladesh, which suggests that, for the sake of child survival, in less developed settings it may be best for women to wait to at least three months before becoming pregnant again following a~~s~~ miscarriage. Steer noted a similar concern in a 2007 editorial in BJOG.[40]

In developed settings, such as that considered in the Love et al. study, there is concern that postponing pregnancies after a miscarriages may lead to difficulties in conceiving and greater

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probabilities of miscarriage because of older women's age. This is less of a concern in poor countries such as Bangladesh, where women begin (and often end) childbearing at earlier ages than in more developed countries.

~~**Conclusion**~~

~~Women who conceive within three months of a miscarriage are more likely to have the subsequent pregnancy result in a live birth. However, the children born after IPIs that began with a miscarriage are more likely to die in infancy if the IPI was very short.~~

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Contributors: JD conceived the study, oversaw the data analysis, and wrote the paper. LH conducted the data analysis and assisted with the writing of the paper. MR designed the data file construction and assisted with the writing of the paper. ~~AR oversaw the construction of the initial data file.~~

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Competing interests: None of the authors has a relationship with any company that might have an interest in the submitted work, and none has any non-financial interests that may be relevant to the submitted work.

Ethical approval: Formal ethical review was not necessary for this study because only anonymised data were analyzed. The data file was created based on records of the Matlab Demographic Surveillance System (DSS) of ~~ICDDR,B~~icddr,b. DSS data collection and management procedures are approved by the ~~ICDDR,B~~icddr,b Ethical Review Committee.

Data sharing: No additional data are available. Permission of ~~ICDDR,B~~icddr,b may be sought to use Matlab DSS data for specific research questions.

Table 1. Demographic characteristics of the sample, by Interpregnancy Interval (-IPI)

IPI duration	Mother's age at miscarriage at beginning of IPI (s.d.)	Mother's age at outcome at end of IPI (s.d.)	MCH-FP Area (%)	Woman has no education (%)*	Gravida =2 (%)	Year 1977-1990 (%)	Year 1991-2000 (%)	Year 2001-2008 (%)	n
≤3 mos.	24.9 (5.8)	25.6 (5.8)	44.3	51.0	27.7	46.3	25.1	28.6	2,138
3-6 mos.	25.5 (6.1)	26.5 (6.0)	45.1	54.0	23.8	50.2	25.3	24.6	2,458
≤6 mos.	25.2 (6.0)	26.1 (6.0)	44.7	52.6	25.6	48.3	25.1	26.5	4,596
6-12 mos.	25.9 (6.4)	27.2 (6.4)	43.4	53.8	24.4	48.0	27.8	24.1	2,920
12-18 mos.	26.7 (6.7)	28.5 (6.7)	45.9	51.1	21.3	44.5	27.3	28.1	988
18-24 mos.	26.9 (6.8)	29.2 (6.7)	46.8	50.3	21.0	37.9	30.5	31.7	676
>24 mos.	27.0 (6.5)	31.5 (6.5)	46.7	50.0	17.4	29.9	34.3	35.8	1,255
24-36 mos.	27.4 (6.8)	30.5 (6.7)	46.6	50.3	17.4	33.2	32.3	34.5	579
36-48 mos.	27.0 (6.5)	31.1 (6.4)	48.6	45.9	18.8	33.2	29.8	37.0	292
>48 mos.	26.5 (6.0)	33.4 (6.0)	45.3	52.6	16.2	22.4	40.9	36.7	384
Total	25.9 (6.3)	27.5 (6.5)	44.8	52.4	23.5	45.0	27.6	27.4	10,435
Significance of differences across expanded IPI categories	P<0.001	P<0.001	ns	P=0.064	P<0.001	P<0.001	P<0.001	P<0.001	

ns = Not significant

* Among those with non-missing values. Education is not reported for 347 cases.

Table 2. Outcomes of subsequent pregnancy after miscarriage in previous pregnancy, by ~~Interpregnancy Interval (~~IPI~~)~~ (n=10,435)

	Outcome of Subsequent Pregnancy						
IPI duration	**Abortion**	**Miscarriage**	**Stillbirth**	**Live Birth**	**Total**	**Col. %**	
≤3 mos.	16	160	87	1,875	2,138	20.5	
(%)	(0.8)	(7.5)	(4.1)	(87.7)	(100.0)		
3-6 mos.	33	262	89	2,074	2,458	23.5	
(%)	(1.3)	(10.7)	(3.6)	(84.4)	(100.0)		
							Love et al. Col. %
≤6 mos.	49	422	176	3,949	4,596	44.0	41.2
(%)	(1.1)	(9.2)	(3.8)	(85.9)	(100.0)		
6-12 mos.	52	302	114	2,452	2,920	28.0	25.2
(%)	(1.8)	(10.3)	(3.9)	(84.0)	(100.0)		
12-18 mos.	25	125	45	793	988	9.5	9.6
(%)	(2.5)	(12.7)	(4.6)	(80.3)	(100.0)		
18-24 mos.	32	81	20	543	676	6.5	6.4
(%)	(4.7)	(12.0)	(3.0)	(80.3)	(100.0)		
>24 mos.	63	173	51	968	1,255	12.0	17.6
(%)	(5.0)	(13.8)	(4.1)	(77.1)	(100.0)		
Total	221	1,103	406	8,705	10,435	100.0	100.0
(%)	(2.1)	(10.6)	(3.9)	(83.4)	(100.0)		
% in Love et al.	(4.9)	(11.7)	(0.6)	(80.3)	(97.5)*		
24-36 mos.	15	66	29	469	578	5.5	
(%)	(2.6)	(11.4)	(5.0)	(81.1)	(100.0)		
36-48 mos.	19	38	9	226	290	2.8	
(%)	(6.5)	(13.1)	(3.1)	(77.9)	(100.0)		
>48	29	69	13	273	384	3.7	
(%)	(7.6)	(18.0)	(3.4)	(71.1)	100.0		

* The Love et al. numbers do not add to 100% because their data also included ectopic pregnancies (0.8% of all outcomes) and "other" outcomes (1.7% of all outcomes).

Table 3. Mortality ~~outcomes~~ after miscarriage in previous pregnancy, by ~~Interpregnancy Interval (~~IPI~~)~~ among all live births (n=8,705) (Mortality rates are calculated using denominator for infants alive and in Matlab at the beginning of the interval~~. [A total of,~~ 284 migrated out before age 1.~~]~~)

	Child's age at death						
IPI duration	**First week**	**Week 2-4**	**Week 5-52**	**Known alive at 1 Year**	**Migrated out before Year 1**	**Total births**	**Col. %**
≤3 mos.	67	37	49	1,647	75	1,875	21.5
(%)	(3.6)	(2.0)	(2.6)	(87.8)	(4.0)	(100.0)	
3-6 mos.	64	26	54	1,868	62	2,074	23.8
(%)	(3.1)	(1.3)	(2.6)	(90.1)	(2.9)	(100.0)	
6-12 mos.	81	28	75	2,196	72	2,452	28.2
(%)	(3.3)	(1.1)	(3.1)	(89.6)	(2.9)	(100.0)	
12-18 mos.	31	8	13	714	27	793	9.1
(%)	(3.9)	(1.0)	(1.6)	(90.0)	(3.4)	(100.0)	
18-24 mos.	18	5	12	496	12	543	6.2
(%)	(3.3)	(0.9)	(2.2)	(91.3)	(2.2)	(100.0)	
24-36 mos.	16	2	7	438	16	469	5.4
(%)	(3.4)	(0.4)	(1.5)	(93.4)	(3.4)	(100.0)	
36-48 mos.	6	2	6	207	5	226	2.6
(%)	(2.7)	(0.8)	(2.7)	(91.5)	(2.2)	(100.0)	
>48	9	2	4	243	15	273	3.1
(%)	(3.3)	(0.7)	(1.5)	(89.0)	(5.5)	(100.0)	
Total	292	110	220	7,799	284	8,705	
(%)	(3.4)	(1.3)	(2.5)	(89.5)	(3.6)	100.0	
Rate per 1,000 at risk	33.5	13.1	26.6				

Figure 1. Relative risk ratios of induced abortion, miscarriage, and stillbirth following a miscarriage by IPI duration: unadjusted and adjusted results from Matlab and Love et al. (2010) (Note: Solid symbols indicate p <0.05)

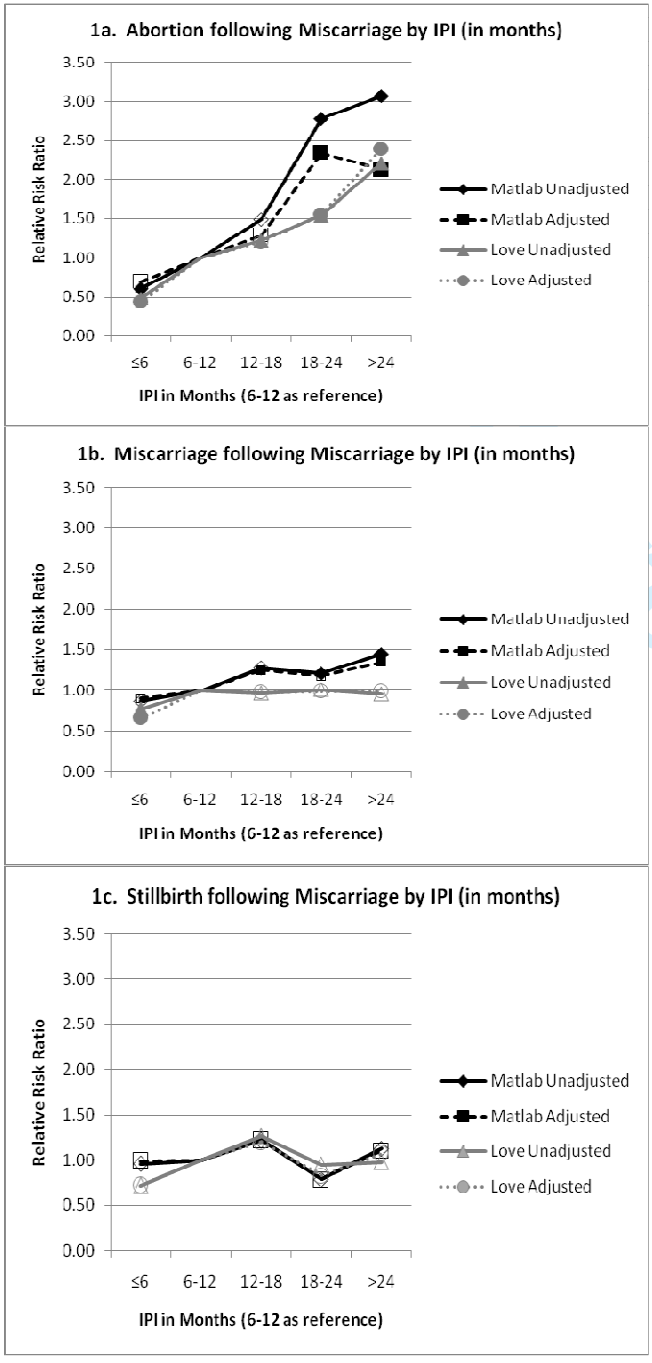
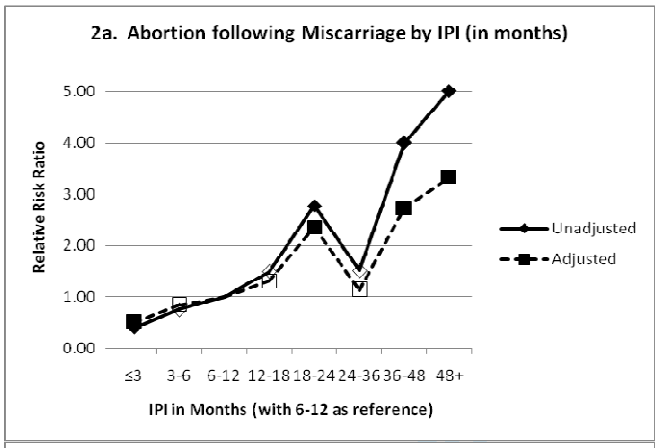
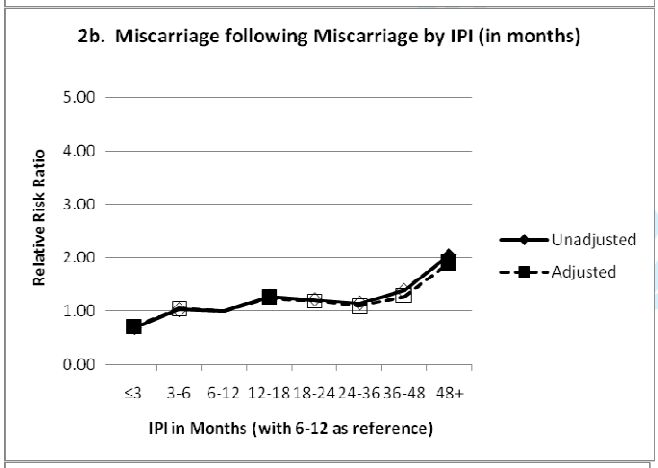


Figure 2. Relative risk ratios of induced abortion, miscarriage, and stillbirth following a miscarriage by expanded IPI categories: unadjusted and adjusted results for Matlab
(Note: Solid symbols indicate p <0.05)





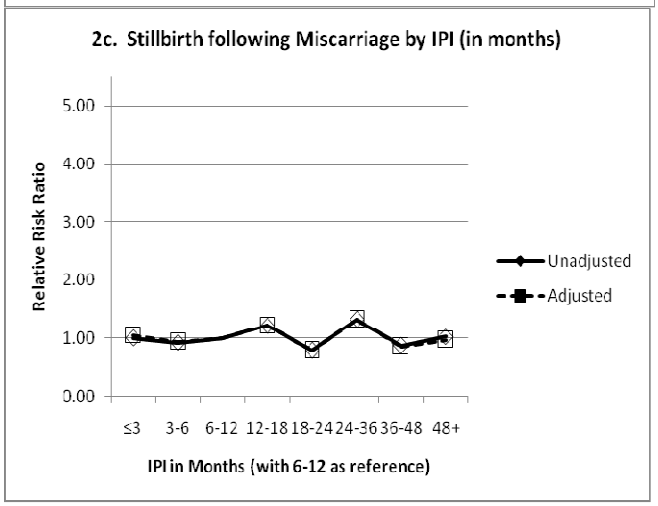
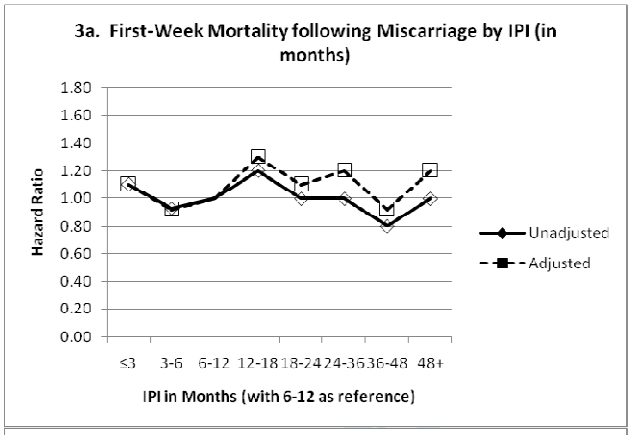
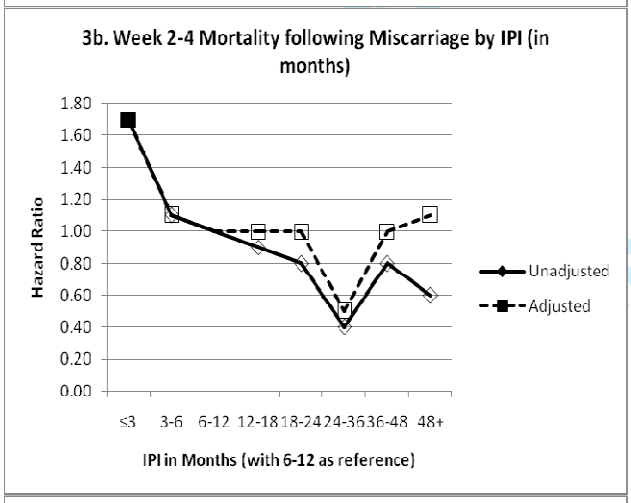


Figure 3. Hazard ratios of mortality during subperiods of infancy, by IPI duration, unadjusted and adjusted results from Matlab (Note: Solid symbols indicate p <0.05)





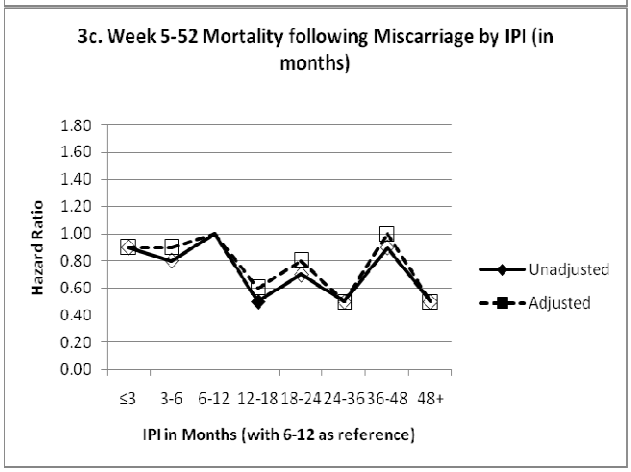


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Figure 1. Relative risk ratios of induced abortion, miscarriage, and stillbirth following a miscarriage by IPI duration: unadjusted and adjusted results from Matlab and Love et al. (2010) (Note: Solid symbols indicate p <0.05)

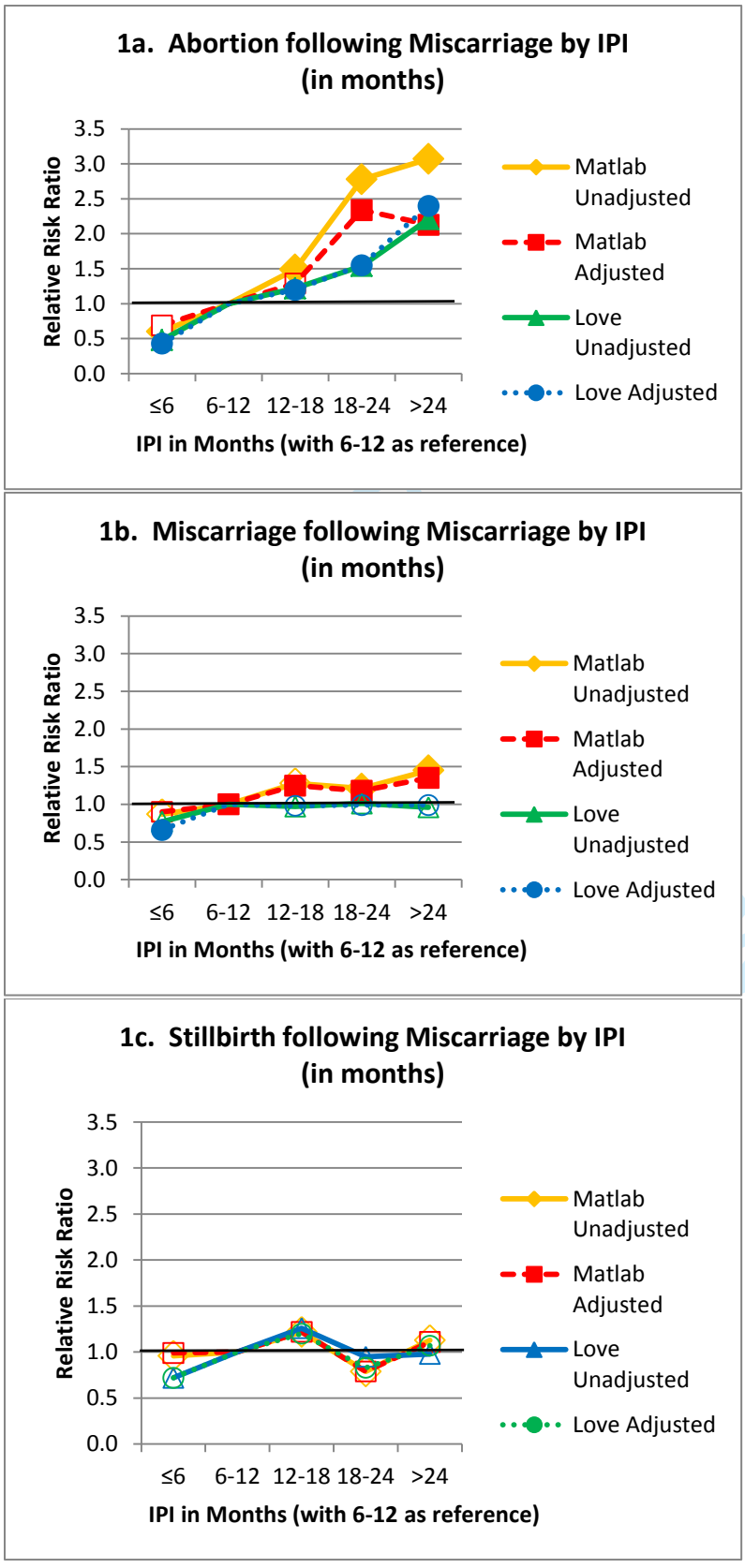
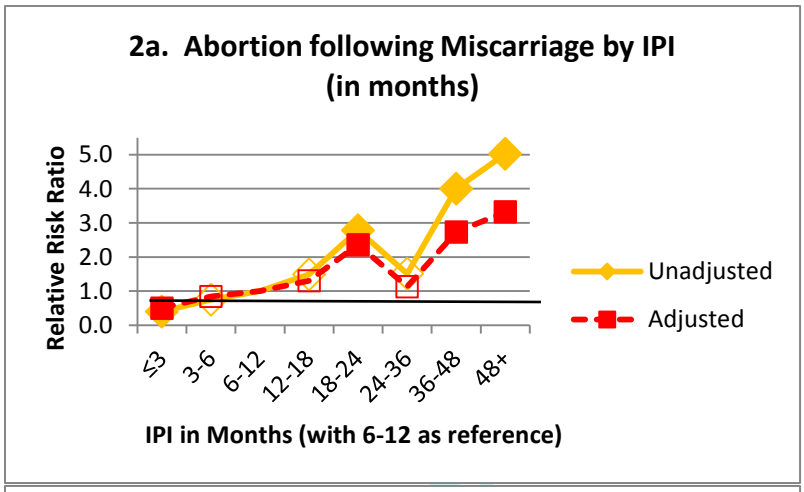
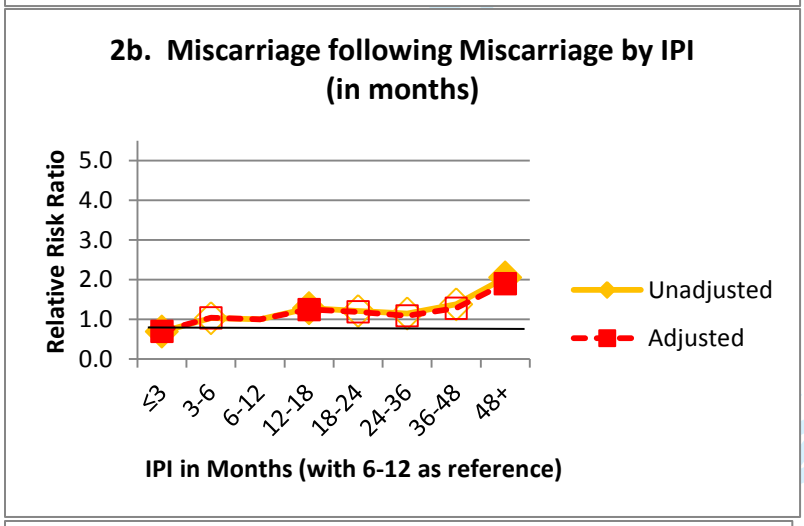


Figure 2. Relative risk ratios of induced abortion, miscarriage, and stillbirth following a miscarriage by expanded IPI categories: unadjusted and adjusted results for Matlab (Note: Solid symbols indicate p <0.05)





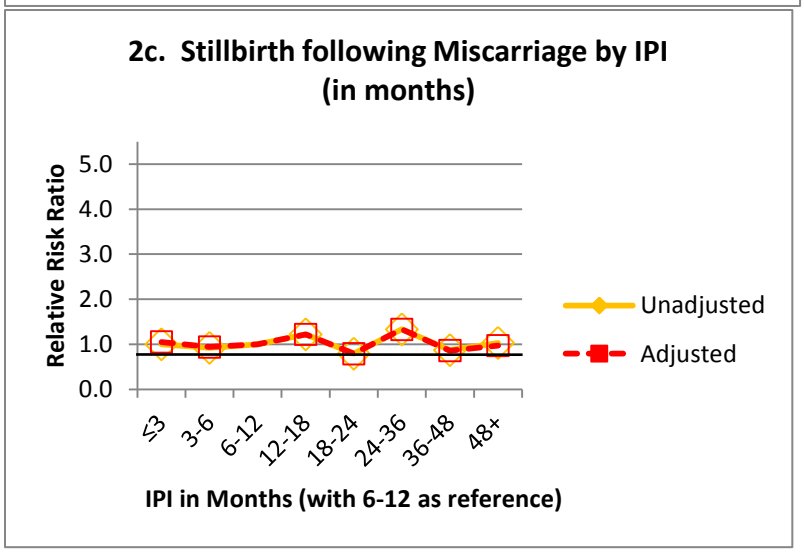


Figure 3. Hazard ratios of mortality during subperiods of infancy, by IPI duration, unadjusted and adjusted results from Matlab (Note: Solid symbols indicate p <0.05)