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Table 2: Mortality rates by time since pregnancy, 1987-2001

Time period	Rate ratio[a]	95% CI	Rate ratio[b]	95% CI	Rate ratio[c]	95% CI
1st trimester	0.68	0.51, 0.90	4.04	3.01, 5.42	3.11	2.32, 4.18
2nd trimester	0.75	0.54, 1.03	4.55	3.26, 6.35	3.55	2.54, 4.96
3rd trimester	1.29	1.00, 1.68	7.70	5.87, 10.10	5.98	4.55, 7.86
Day of birth	38.63	25.87, 57.68	231.61	154.04, 348.23	180.31	119.74, 271.52
Day 1 postpartum	18.48	11.56, 29.55	62.90	39.26, 100.78	54.93	34.26, 88.06
Day 2	8.05	4.17, 15.56	21.78	11.26, 42.12	21.07	10.90, 40.76
Days 3 to 7	5.80	4.02, 8.38	17.87	12.35, 25.84	16.07	11.10, 23.25
Weeks 2 to 6	2.29	1.81, 2.89	7.93	6.27, 10.05	6.94	5.48, 8.80
Weeks 7 to 12	0.86	0.61, 1.19	2.68	1.92, 3.75	2.38	1.70, 3.33
Weeks 13 to 52	0.49	0.40, 0.59	1.59	1.29, 1.95	1.40	1.14, 1.73
1 to 2 years	0.55	0.46, 0.66	1.47	1.22, 1.78	1.34	1.11, 1.62
2 to 3 years	0.48	0.38, 0.60	1.11	0.88, 1.40	1.03	0.82, 1.29
3 to 4 years	0.65	0.52, 0.81	1.13	0.90, 1.41	1.09	0.85, 1.34
4+ years	1.00	-	1.00	-	1.00	-
Never pregnant	1.45	1.31, 1.61	9.68	8.61, 10.88	5.13	3.98, 6.61
No pregnancies during study	1.89	1.71, 2.09	2.40	2.15, 2.67	2.11	1.89, 2.36

[a] Crude rate ratio
[b] Rate ratio adjusted for age
[c] Rate ratio adjusted for age, parity, area of residence and marital status at entry

Figure 1: Crude mortality rates, by time since pregnancy

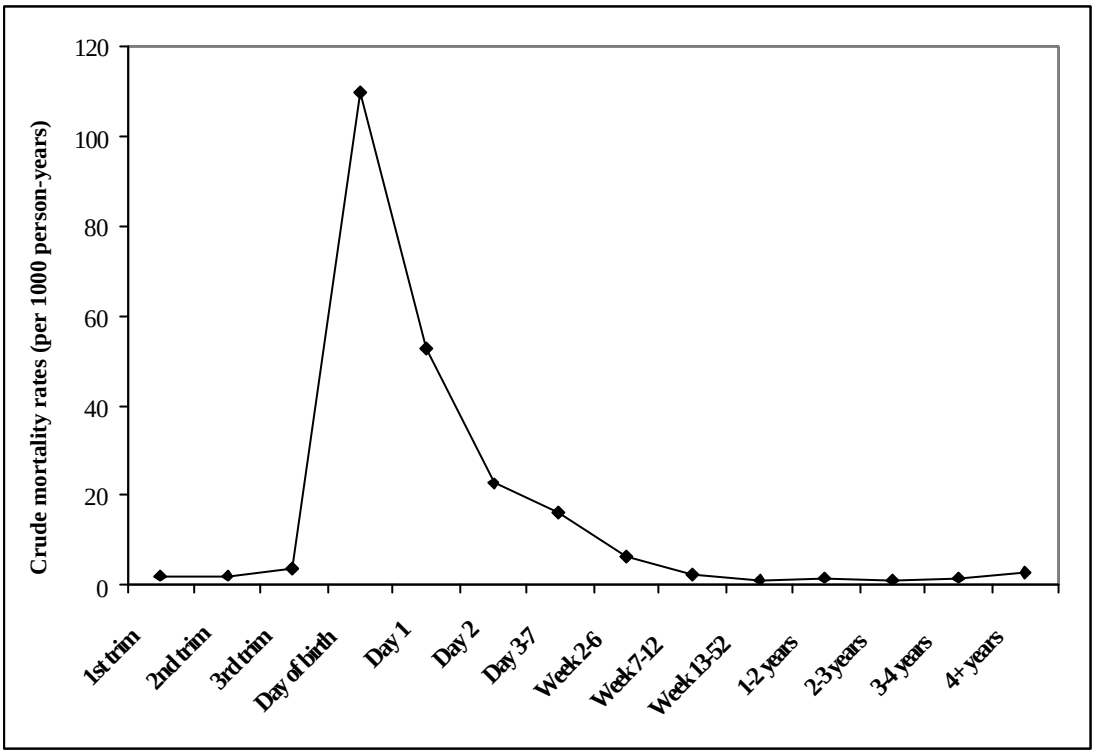

Table 1: Mortality rate and rate ratios comparing women who experienced pregnancies during this study with women who had never been pregnant and women who were not pregnant during this study but were parous

	Pregnant during study	Gravid but not pregnant in this study	Never pregnant
Deaths	65	1795	1030
Person-years	13888	29318	24910
Mortality rates (per 1000 person-years)	0.47	6.12	4.13
Crude rate ratio (95% CI)	1.00	13.08 (10.21, 16.76)	8.83 (6.88, 11.35)
Rate ratio, adjusted for age (95% CI)	1.00	1.32 (1.01, 1.72)	9.13 (7.05, 11.82)
Rate ratio, adjusted for age, parity, area of residence, marital status (95% CI)	1.00	1.61 (1.17, 2.23)	6.50 (4.24, 9.97)

with further research on the physiological factors that may mediate such associations, these data could be of great importance in the appropriate design and delivery of postpartum services in this setting.

(such as anaemia after severe blood loss) may also have long-term sequelae but the empirical evidence in support of their contribution to mortality is weak (AbouZahr 1999). There is, therefore, no one obvious factor that can be shown to mediate these postpartum risks and further research is required to examine the physiological changes associated with pregnancy that may lead to such persistently elevated mortality in the years following a pregnancy.

Finally, a further unique feature of our data was that we were able to examine the mortality of never-pregnant women separately in our analyses. After adjusting for potential confounders, these women had significantly higher mortality than women who were pregnant during the follow-up period or who had previously experienced pregnancies. This may be expected in a setting such as Bangladesh where very few women remain childless. Women with no children may therefore have higher mortality because of the social exclusion faced by women who fail to conceive. However, it may also be the case that this data provides further evidence for a "healthy pregnant woman effect" by showing, consistent with other studies (Khlat and Ronsmans 2000; Ronsmans et al. 2001), that women who are healthier or in some way stronger are more likely to be fertile than women who are ill or in some way weaker.

CONCLUSION

Our results show that mortality in women in rural Bangladesh remains elevated for longer than the conventional 42 days used in the definition of maternal mortality. We are hoping that further adjustments and stratifications will help us to build a clearer picture of the postpartum risk period in women in rural Bangladesh. Taken together

for potential confounders however, and our adjusted results are also consistent with previous data from rural Bangladesh which showed increases in mortality following pregnancy up to two years after the birth (Menken et al. 2003). The advantages of our data were a larger sample size, allowing for a finer division of time scales (this will be particularly important when we examine for effect modification), information on all pregnancies instead of only live births and sufficient information to examine never-pregnant women as a separate group.

To interpret our data, we need to examine whether there are obvious physiological explanations for such prolonged periods of elevated mortality. The postpartum risk period as conventionally defined is largely based on the timing of involution of the uterus, while also being sanctioned by religious and cultural practices (Campbell and Graham 1990; Hundt et al. 2000). Other physiological changes associated with pregnancy vary in the time that they take to return to pre-pregnancy levels. For example, haemo-dynamic balance is fully restored after delivery and hormone levels and glucose tolerance return to normal in the immediate postpartum (Cunningham et al. 1999). However, although cell-mediated immunity is fully restored after delivery, women may remain exposed to the foetal antigens forever - with possible implications for long-term mortality risks (Perks and Coulton 2001). The length and intensity of breastfeeding may also affect women's health and survival after birth. It has been estimated that an additional intake of between 500 and 1000 calories a day are required to maintain an adequate nutritional state when feeding a child on the breast (Jelliffe and Jelliffe 1978). It is thus possible that breast feeding has an important and sustained influence on postpartum mortality risk, particularly in poor and malnourished populations such as those in Bangladesh. Some obstetric complications

Attribution of cause of death is difficult in settings like Matlab, in the absence of accurate data from pathological tests and autopsies. Although our data will not therefore allow for a breakdown of deaths by specific cause, we are hoping to stratify the analyses by broad groupings of causes to examine whether the patterns vary by group. In studies of deaths occurring between 42 days and one year postpartum, between 7 and 50 percent were thought to result from the pregnancy, and most of these are thought to be indirectly linked to the pregnancy (Gissler et al. 1997; Health 1998). However, the interaction between pregnancy and these indirect causes of death remains poorly understood. For example, although there is little evidence that illnesses such as tuberculosis and HIV progress more rapidly in pregnant women, the postpartum period during which women remain at risk of mortality may be extended in women who suffer from such chronic infectious illnesses. We therefore hope to gain an understanding of how patterns in mortality vary by time since pregnancy according to cause, by examining deaths from indirect causes separately from direct causes. Mortality in the early stages of pregnancy was elevated in our data, a probable artefact of including deaths in undelivered women and deaths from abortions in the trimester in which they occurred. Deaths following an induced abortion, in particular, may have a different pattern and a separate analysis of these is also planned.

Despite the fact that our analyses are incomplete, the data presented are consistent with previous studies that have examined mortality by time since pregnancy. Our crude data suggest increased mortality until the twelfth week postpartum, as did those obtained in the Nepalese study in which there was no adjustment for potential confounders (Pradhan et al. 2002). Our estimates changed dramatically after adjusting

somewhat, as unidentified pregnancies that did not end in a death would not have been added. Whilst we know that a proportion of pregnancies (and pregnancies that end early on in particular) will remain unidentified whether the women survive or die, there are probably fewer unidentified pregnancies in women who survived, and our additions are unlikely to bias the results excessively. In addition, since the date of birth of the child and the date of death of the mother are known from these previous studies, adding these pregnancies should not change the patterns in mortality by time since pregnancy but merely inflate the mortality rates at each time interval.

Our analyses of these data are not yet complete. Although we were able to adjust for several potential confounders in this study, we have not yet merged all of the socio-economic data from the censuses (including data on education, occupation and wealth) with the pregnancy files. There may therefore be some residual confounding by socio-economic status in our data, as fertility and mortality share many common socio-economic determinants. This confounding is again unlikely to change the patterns in mortality by time since pregnancy (particularly as other factors indicative of socio-economic status such as parity and marital status had a minimal effect), but will most likely change the magnitude of the effects seen.

We are also interested in examining whether the patterns seen by time since pregnancy modify according to both socio-demographic and reproductive factors. For example, it is plausible that mortality may remain high for longer periods of time in older women, those of very high parity or those with short spaces between the index pregnancy and the previous pregnancy. Examining for interaction will therefore be an important next phase of analysis.

women who did not experience any pregnancies during the study period but for who their time since last pregnancy was unknown had a two fold increase in mortality.

DISCUSSION

Our analysis shows that, when patterns in mortality by time since pregnancy were examined, there was a significantly increase in all-cause mortality during pregnancy, and on the day of birth in particular, compared with women who were four or more years since their most recent pregnancy. After adjusting for age, mortality risks remaining elevated until the end of the second postpartum year.

The quality of the data used in this study is known to be very high. The HDSS is a unique dataset, providing longitudinal data on all births, deaths, marriages and migrations in Matlab since 1966 (Fauveau 1994). It is one of the few high-quality sources of data for longitudinal studies in the developing world and has been used extensively in the demographic literature. In a previous validation study, only three percent of women reported a different number of children to that recorded in the HDSS and four percent reported a different number of child deaths (Becker and Mahmud 1984). However, even within the intensive surveillance conducted at Matlab, deaths during pregnancy are known to be underestimated (Ronsmans et al. 1998). We were thus fortunate to have access to data from special studies conducted in the Matlab area to identify all maternal deaths within the HDSS area. These studies recorded information on the date of birth of the child, the date of death of the mother and the cause of death, so that we were able to add an appropriate pregnancy record where there was no pregnancy recorded in the HDSS. It is important to note that by doing this we may have inflated the number of deaths associated with pregnancy

more years after the pregnancy (presumably because women were then becoming older).

The rate ratios by time since pregnancy, relative to women four or more years since their previous pregnancy, are shown in Table 2. The crude rate ratios are presented first, followed by the ratios adjusted for age and then the ratios adjusted for age and other socio-demographic factors. Again, adjusting for age had the most dramatic effect on the results, with most rate ratios increasing after this adjustment and those up to two years postpartum becoming statistically significant. Adjusting for other socio-demographic factors (parity, area of residence and marital status at entry) reduced the age-adjusted rate ratios slightly, although none of these factors produced great changes on their own. Once adjusted for age and the socio-demographic factors, mortality was three times higher during the first and second trimesters of pregnancy compared with women four or more years postpartum, and almost six times higher in the third trimester. The most risky day for women remained the day of birth when mortality was almost 200 times higher than for women four or more years after a pregnancy (adjusted RR 180.31, 95 percent CI 119.74-271.52). Women between seven and 12 weeks postpartum had a more than two-fold increase in mortality (adjusted RR 2.38, 95 percent CI 1.70-3.33). Women between 13 and 52 weeks had a significant 40 percent increase in mortality (95 percent CI 1.14-1.73) and women in their second year postpartum had a significant 34 percent increased mortality (95 percent CI 1.10-1.62).

Compared with women who were four or more years since their previous pregnancy, never-pregnant women had a significant five-fold increase in mortality, and gravid

were gravid (having experienced at least one pregnancy previously). Crude mortality rates were lowest in women who experienced a pregnancy during the follow-up period and highest in women who did not (Table 1). Mortality rates in the never-pregnant were also high, lying between those of women in the two other groups. However, nulligravid women may have been younger than gravid women, as they may not yet have begun their reproductive careers. Conversely, gravid women who did not have a pregnancy during the study period may have been older than women experiencing pregnancies, as they may be coming to the end of their reproductive lives. Adjusting for the potential confounding effects of age was therefore particularly important. Once we performed this adjustment, women who did not have any pregnancies during the study period still had significantly higher mortality than the women who experience a pregnancy, but the magnitude of the rate ratio was reduced (age-adjusted rate ratio (RR) 1.32, 95 percent confidence interval (CI) 1.01, 1.72). The never pregnant, on the other hand, had a significant nine-fold increase in mortality when compared with women pregnant during the study period (age-adjusted RR 9.13, 95% CI 7.05, 11.82). Further adjustment for parity, area of residence and marital status increased the estimates slightly for women who did not have pregnancies during the study period (adjusted RR 1.61, 95% CI 1.17, 2.23), but reduced the rate ratio in never-pregnant women to 6.50 (95% CI 4.24, 9.97).

Figure 1 shows crude mortality rates during pregnancy and by time since pregnancy. These rates increased gradually as women passed through each trimester of pregnancy, and increased dramatically around the time of delivery. Mortality rates remained elevated until the 12th week postpartum, although their magnitude reduced with time. After this, rates remained relatively consistent with a slight increase again four or

socio-demographic factors, with the rate ratios examined after adjusting for each separate factor to look for evidence of confounding.

Sample size

Sample size calculations were based on the method for the comparison of rates given by Kirkwood (1988)[37]. The estimates were all based on having a power of 90% to detect differences with a significance level of 5%. With the number of pregnancies available and assuming a mortality rate of 4.5 per 1000 person years in pregnant women overall (Khlat and Ronsmans 2000), there was a sufficient sample size available to detect a 25% excess (rate ratio of 1.25) in the mortality rates in pregnant women compared with the non-pregnant (unexposed) women, as well as a sufficient sample size to detect a modification in the magnitude of the excess mortality during pregnancy on stratification by other factors (Kirkwood 1988).

RESULTS

120,405 women were eligible for entry into the cohort. Details of reproductive history on entry into the cohort were missing for 1026 (1 percent) entries. 989 women had no recorded reproductive history at all and 37 women entered at another point in time with a known reproductive history. All entries for which reproductive history on entry was not known were excluded from all further analyses, leaving 119,416 women and 1,045,131 person-years of follow-up. The crude all-cause mortality rate in the cohort was 3.42 per 1000 person-years (95% CI for rate 3.31-3.54).

There were 94,533 pregnancies in 43,992 women during the follow-up period. Of the 75,424 women who had no pregnancies, 50,718 had never been pregnant and 24,706

Statistical analyses

Individual pregnancy records were linked with death records, using the mother's unique identification number, to obtain information on mortality during pregnancy, by time since pregnancy and in never-pregnant women. Follow-up was divided into relevant periods of exposure (each trimester of pregnancy, then by day around the time of birth and in the first week postpartum, by week until 12 weeks postpartum, by month from 3 months to 1 year postpartum, and each year thereafter). Where women died before delivery or following a spontaneous or induced abortion, no date of birth was specified (as there is no pregnancy outcome in undelivered women and the date of pregnancy outcome is often not known following an abortion). Instead, these were categorised as deaths in the appropriate trimesters of pregnancy without a separate date of birth. For example, deaths following an induced abortion were classified as deaths within the first trimester.

Women-years of observation were summed within each exposure and covariate category to obtain denominator figures. All-cause mortality rates in each exposure period were then calculated. Crude mortality rates were examined, and time periods with similar rates were grouped together in order to increase the precision of the estimates obtained from the multivariate models. Rate ratios were calculated using Poisson regression. Women who were 4 or more years after a pregnancy were used as the baseline group, so that patterns in mortality in the years following the pregnancy could be examined as well as mortality in the first days and weeks postpartum. Random effects Poisson models were used to account for the fact that observations were not always independent of each other (as women could have several pregnancies during the study period). Analyses were adjusted for maternal age, parity, and other

Study population and data

Our study population includes all women aged 12 to 45 years living in the Matlab surveillance area between 1987 and 2001. We selected January 1st 1987 as the start date for the analyses presented here as the additional data on maternal deaths mentioned above are also available from this date. The data on maternal deaths obtained from the HDSS has therefore been checked for completeness and pregnancy records updated where necessary. (Similar data are also available for the period between 1976 and 1986, although this information is less complete. It is hoped that this data will also be added to our analyses in the coming months.) All subjects were followed up from the day they entered until they died, migrated or until December 31st 2001.

Data on all pregnancies in the HDSS area between the census in 1974 and our entry date were also available. These data were not used for this analysis, as the data checking and cleaning for this time period is not yet complete. However, it was possible to use this data to estimate the time since a previous pregnancy for women entering our cohort on January 1st 1987 if they were resident in the HDSS area during their previous pregnancy. For women who migrated into the area during the study period, we had information on their reproductive histories but not on the dates of their previous pregnancies. We were therefore able to identify which of these women were nulligravid. However, we did not know the date of the last pregnancy for gravid women who migrated into the area during the study period. They were therefore included in our models as a separate category (gravid but no pregnancies during the study period), contributing person-time data to the time since pregnancy categories if they became pregnant during the study period.

METHODS

Study design and setting

This is a historical cohort study using longitudinal data from Matlab, Bangladesh between 1987 and 2001. Matlab is a rural area situated on the Ganges-Meghna floodplain. A significant demographic transition has occurred in the area over the past 20 years, with a rapid decline in both fertility and mortality. The current total fertility rate is around 2.27 births per woman and average life expectancy for women is 58 years (Mitra et al. 1997). Maternal mortality remains high in the area, although it has declined steadily between the late 1970's and 2001 (BMMS 2002).

The ICDDR, B: Centre for Health and Population Research (ICDDR, B) has maintained a Health and Demographic Surveillance System (HDSS) in Matlab since 1966, covering a population of approximately 200,000 individuals. Female community health workers (CHW) visit each house in every village monthly to collect the data. Senior health assistants also visit the villages every two months, to verify the data collected. All pregnancy outcomes (live births, still births, spontaneous abortions), marriages, migrations and deaths are recorded, with verbal autopsies used to determine causes of death. The population base for the HDSS is updated using periodic censuses, which also supplement the demographic data with other data on other factors including religion, education and occupation. Special in-depth studies have also been conducted within the HDSS area, to identify all deaths in women of reproductive age and to ascertain whether the women were pregnant when they died (Koenig et al. 1988; Ronsmans et al. 1997).

the never-pregnant, women between pregnancies and women who had stopped childbearing and partly because each study only had information on live births.

A study from Nepal extended this epidemiological approach to maternal deaths by comparing all-cause mortality rates during pregnancy and by time since the pregnancy outcome (Pradhan et al. 2002). Mortality rates in different time periods were compared with mortality rates in women who were 52 weeks or more after their most recent pregnancy. Mortality is significantly higher in women between the onset of labour and seven days postpartum and between week two and week six postpartum than in women who were a year or more postpartum. There was also some suggestion that mortality is higher in women who were between seven and 12 weeks postpartum, but this rate ratio was not statistically significant. There was also no adjustment for potential confounders in this study.

The objective of our research is to build on the results of these previous studies, to improve our understanding of the relationship between pregnancy and mortality in the months and years after birth. We have analysed a unique data set from Bangladesh to compare all-cause mortality rates at different times during and following pregnancy, and in never-pregnant women. The study has a large sample size and we have data on all pregnancies in a defined area within a defined period of time (not only live births). There is also information on numerous potential confounders in the dataset, and we can examine whether associations change after adjusting for these demographic and socio-economic factors.

uncertainties about the length of the postpartum risk period were acknowledged, and the concept of "late" maternal deaths was introduced (WHO 1992). This refers to deaths from direct or indirect obstetric causes more than 42 days but less than one year after the termination of the pregnancy.

Nevertheless, the length of the postpartum period during which women remain at increased risk of mortality remains uncertain because few studies have addressed the issue of causality in the context of pregnancy-related mortality using an epidemiological approach - by comparing mortality during pregnancy (an exposed period) with mortality outside that period (an unexposed period). Two studies in Finland and the US compared mortality within a year of a birth with mortality in women without a recent pregnancy (Gissler et al. 1997; Jocums et al. 1998) and found that the age-adjusted risks of death from all causes are lower within a year of a birth than in women without a recent pregnancy. Similarly, two studies in Bangladesh (Khlat and Ronsmans 2000) and Senegal (Ronsmans et al. 2001) compared mortality in pregnant women or within 90 days after birth with women who were outside that period. In Bangladesh, pregnant or recently delivered women are twice as likely to die from all causes as women who were outside that period, while no differences were observed among Senegalese women. A further small study in Bangladesh showed that women who have experienced a live birth in the past two years have twice the mortality of women who did not have a live birth, independent of parity or the pace of childbearing (Menken, Duffy and Kuhn 2003). These findings suggest that the conventional 42-day risk period may not be appropriate for all settings. Their interpretation is also complex however, partly because the comparison groups include

Pregnancy and the postpartum are often represented as vulnerable periods in a woman's life, either because pregnancy leads directly to mortality (direct obstetric deaths) or because pregnancy is thought to aggravate underlying disease conditions (indirect obstetric deaths). However, despite growing attention to the problem of maternal mortality worldwide, many uncertainties remain as to the nature and magnitude of mortality associated with pregnancy. In particular, a difficult and unresolved issue is the definition of the length of time after delivery during which pregnancy-associated risks persist. It is generally thought that the adverse effects associated with pregnancy extend up to at least six weeks postpartum, although longer term effects have also been suggested, particularly after numerous and closely spaced pregnancies. However, few studies provide epidemiological evidence in support of such medium or long-term effects.

BACKGROUND

The definition of a maternal death is surprisingly complex owing, in part, to the difficulties in distinguishing between the risks attributable to childbearing and the risks of coincidental diseases, and to uncertainties about the length of time postpartum during which risks persist (Campbell and Graham 1990). In the Ninth Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (WHO 1977), a maternal death is defined as "*the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes*". Others have suggested, however, that maternal deaths may occur up to 90 or 120 days postpartum (Committee on Maternal and Child Care 1964; Shanklin et al. 1991). In the ICD-10, the

SUMMARY

Pregnancy and the postpartum are often represented as vulnerable periods in a woman's life, but many uncertainties remain as to the nature and magnitude of mortality associated with pregnancy. We conducted a historical cohort study in Matlab, rural Bangladesh to examine mortality rates by time since pregnancy and to assess whether women remain at risk of mortality for longer periods than those used in conventional definitions of maternal deaths. We found that mortality was significantly higher in women up to two years postpartum when compared with women who were four or more years after their previous pregnancy. Further analyses on these data that may aid in the interpretation of the results are analyses stratified by socio-demographic and reproductive factors and analyses stratified by cause of death. Further studies are also required examining the physiological changes which may be mediating these associations. Taken together, these data could then aid in the appropriate design and delivery of postpartum services in this setting.

Mortality by time since pregnancy in women of reproductive age in rural Bangladesh

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