Risk of death following pregnancy in rural Nepal
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Objective To investigate the length of time following pregnancy during which the risk of mortality was elevated among women in rural Nepal.

Methods An analysis was performed of prospective data on women participating in the control group of a large, population-based trial. Weekly visits were made for three years to 14,805 women aged 14–45 years. Pregnancy and vital status were assessed. A total of 7325 pregnancies were followed. Mortality during and following pregnancy, expressed on a person-time basis, was compared to referent mortality unrelated to pregnancy (>52 weeks after pregnancy) in the same cohort.

Findings The relative risk (RR) of death during pregnancy but before the onset of labour was 0.93 (95% confidence interval (CI): 0.38–2.32). During the perinatal period, defined as lasting from the onset of labour until seven days after outcome, the RR of death was 37.02 (95% CI: 15.03–90.92). The RR for 2 to 6 weeks, 7 to 12 weeks, and 13 to 52 weeks after pregnancy were 4.82, 2.59 and 1.01 with 95% CI of 1.77–13.07, 0.81–8.26 and 0.40–2.53, respectively. The RR of death was 2.21 (95% CI: 1.03–4.71) during the conventional maternal mortality period (pregnancy until 6 weeks after outcome). It was 2.26 (95% CI: 1.05–4.90) when the period was extended to 12 weeks after pregnancy outcome.

Conclusion The risk of mortality associated with pregnancy should be assessed over the first 12 weeks following outcome instead of over the first 6 weeks.

Keywords Maternal mortality; Pregnancy complications/mortality/etiology; Puerperium; Risk factors; Prospective studies; Cohort studies; Nepal (source: MeSH, NLM).

Mots clés Mortalité maternelle; Grossesse compliquée/mortalité/étiologie; Puerperalité; Facteur risque; Etude prospective; Etude cohorte; Népal (source: MeSH, INSERM).

Palabras clave Mortalidad materna/Complicaciones del embarazo/mortalidad/etiología; Puerperio; Factores de riesgo; Estudios prospectivos; Estudios de cohortes; Nepal (fuente: DeCS, BIREME).

Introduction
WHO estimates that some 515,000 women die annually from pregnancy-related causes during the period including pregnancy and the six weeks postpartum, nearly all in the developing world (1). The need for accurate measurement of the risk of such mortality has raised questions about the adequacy of the conventional 42-day postpartum period of risk used to define maternal death (2,3). It has been suggested that the period for calculating the risk of maternal mortality should be extended to 12 weeks. However, concern has been expressed that this would reveal only a very small percentage of deaths attributable to pregnancy and its complications (4,5). In recent years, WHO’s International Classification of Diseases (ICD-10) has introduced two additional definitions to accommodate measures of extended maternal risk: a late maternal death occurs more than 42 days but less than a year after the outcome of pregnancy and is attributable to direct and indirect obstetric causes; a pregnancy-related death occurs within the conventional six-week interval but includes deaths from all causes during pregnancy and until 42 days (six weeks) postpartum (6). Few population-based data exist on the length of time during which the risk of mortality remains elevated following pregnancy outcome (7). Information of this kind permits an objective assessment of the usefulness of an extended period for reflecting pregnancy-related risk. In order to investigate this issue we analysed prospective, population-based survival data from a large cohort of women of childbearing age who participated in a community intervention trial on the rural plains of Nepal. We hypothesized that the risk of pregnancy-related death (i.e. deaths from all causes following pregnancy outcome) might extend beyond six weeks after the outcome of pregnancy.

Methods
The study involved an assessment of the vital experience of women participating in a control group of a large micronutrient supplementation trial conducted in Sarlahi, Nepal from 1994 to 1997. The design and procedures of the trial have been described elsewhere (8). It was a randomized, double-masked, community-based, placebo-controlled trial that assessed the efficacy of a weekly dose of vitamin A or beta-carotene in reducing maternal
and infant mortality. The dose is given at recommended dietary levels to women throughout the childbearing years. The study was conducted in 270 wards in the southern plains of Nepal, with a total population of approximately 186,000 living in an area of about 400 km² contiguous with and culturally similar to the northern Gangetic plains of India. Eligible women received a weekly supplement containing vitamin A (7000 μg retinol equivalents), beta-carotene (42 mg) or placebo in 90 wards selected at random for each treatment. A total of 44,646 married women of reproductive age, including 14,805 in the placebo group, participated in the trial, among whom menstrual status, pregnancy occurrence and vital events were tracked on a weekly basis. Verbal consent was provided by women before their enrolment in the study. Over 22,000 pregnancies were identified and placebo was administered in 7325 of them.

The women were observed until loss to follow-up, death, or the ending of the trial. Deaths of enrolled women were investigated by conducting lay verbal autopsy interviews with family members of the deceased. Causes of death were assigned by two medical doctors on the basis of the results of these interviews. Verbal autopsy data are used in the present study to differentiate between deaths unrelated to injury (i.e. caused by illnesses) and those that were attributable to intentional or non-intentional injury. After approximately three years of observation there were reductions of 40% and 49% in the mortality of illnesses) and those that were attributable to intentional or non-

Mortality rates were calculated for the conventional pregnancy-related death interval, i.e. including pregnancy and the 6 weeks postpartum in the vitamin A and beta-carotene groups respectively in comparison with the placebo group (8). No reduction was observed in fetal or infant mortality (9).

Because of the substantial decrease in pregnancy-related mortality in both treatment groups, the analysis in the current study was restricted to participants receiving placebo. They provided the closest possible representation of women of childbearing age in this poor rural part of southern Asia, for whom no micronutrient supplementation programmes were available. We compared the risk of death in the period including pregnancy and (i) the six weeks following pregnancy outcome and (ii) the late maternal period, stratified into intervals of 7–12 and 13–52 weeks after pregnancy outcome, with that in a referent period representing non-pregnancy mortality, i.e. more than 52 weeks after pregnancy occurrence and vital events were tracked on a weekly basis. The cohort under study comprised women participating in the control group of the supplementation trial (8) who had a pregnancy outcome between 18 July 1994 and 29 July 1997.

A pregnancy reported by a woman during weekly surveillance was counted if it ended in a reported miscarriage, live birth or stillbirth, irrespective of the stage at which it was reported. A pregnancy reported by a woman on at least six consecutive weeks of home visits, for which an explicit outcome was not reported, was considered to be an eligible pregnancy that ended in early miscarriage. A report of a pregnancy on fewer than six consecutive weeks of home visits without a reported outcome was defined as a false-positive report and excluded from the analysis.

In order to explore the gradation of risk during pregnancy, childbirth and the weeks following pregnancy outcome, mortality rates were calculated for six mutually exclusive time intervals:

1. pregnancy up to the time of labour;
2. a perinatal period from the onset of labour until day 7 following pregnancy outcome, or, in the case of a miscarriage with no onset of labour, from pregnancy termination until day 7 following it;
3. week 2 to week 6 following outcome;
4. week 7 to week 12 following outcome;
5. week 13 to week 52 following outcome;
6. the referent period (more than 52 weeks after pregnancy outcome).

Mortality rates were calculated for the conventional pregnancy-related death interval, i.e. including pregnancy and the 6 weeks following pregnancy outcome. The late maternal period of 7–52 weeks after pregnancy outcome was partitioned into 7–12 and 13–52 weeks post-outcome in order to explore risk differences within this time period. The choice of these two strata was guided by supplementation impact findings (8) and by concerns about precision because of the rare occurrence of late pregnancy-related death.

Mortality rates were computed as the number of deaths per 100,000 person-years of observation in each time interval. Rates, relative risks (RR) and 95% confidence intervals (CI) were calculated using Stata 6.0 (Stata Corporation, College Station, Texas). Each CI was widened to account for the ward, rather than the individual, being the unit of randomization (8, 10, 11). Adjustment for this design effect required a 10% inflation of the width of all CI, in the natural logarithm, for RR estimates.

The original trial protocol was reviewed and approved by the Nepal Health Research Council in Kathmandu, Nepal, and by the Joint Committee on Clinical Investigation of the Johns Hopkins School of Medicine and the Teratology Society, Bethesda, Maryland, USA.

Results

Of the 14,805 women in the placebo group, 6101 contributed 7325 pregnancies to the study. There were 589 miscarriages/stillbirths and 6718 live births, and 18 women died while pregnant, 16 before the onset of labour and 2 after labour began. The mean number of years of observations per woman was 2.34 (standard deviation (SD) = 0.7) and the mean numbers of weeks of observation in the period of the pregnancy plus 6, 7–12 and
13–52 weeks postpartum were 43.03 (SD = 5.36), 5.86 (SD = 0.86), and 32.20 (SD = 12.84), respectively. The mean period of observation in the referent interval (beyond 52 weeks postpartum) was 28.6 (SD = 32.21) weeks. The number of pregnancies enrolled has changed slightly since the study was first published (8). A refined estimate of the date of pregnancy outcome resulted in the inclusion of 84 pregnancies that had previously been outside the cut-off date.

Data on the causes of mortality are given in Table 1. The RR are depicted in Fig. 1. Beyond 52 weeks postpartum the mortality rate was 328 per 100 000 person-years (relative risk 1.00). During pregnancy but before the onset of labour the mortality rate was 306 per 100 000 person-years, which was comparable to that during the referent interval (RR 0.93, 95% CI 0.38–2.32). In the perinatal period the mortality rate was 12 143 per 100 000 person-years; this was a period of extremely high risk (RR 37.02, 95% CI 15.30–90.92). The rate dropped to 1580 deaths per 100 000 person-years in the 2–6 weeks following pregnancy outcome (RR 4.82, 95% CI 1.77–13.07). In weeks 7–12 after outcome the mortality rate was 848 per 100 000 person-years, over twice as high as in the referent interval (RR 2.59, 95% CI 0.81–8.26). Beyond 12 weeks after pregnancy outcome the observed rate of 331 deaths per 100 000 person-years was comparable to that of the referent interval (RR 1.01, 95% CI 0.40–2.53).

The mortality rates for the successive periods (Fig. 2) suggest that there are two periods of distinctly different risk in this population. In the period including pregnancy and the 6 weeks following pregnancy outcome the mortality rate was 726 per 100 000 (RR 2.21, 95% CI 1.03–4.71, compared to the referent interval). The high overall mortality rate of 741 per 100 000 and the relative risk (2.26, 95% CI 1.05–4.90) remained unchanged when the interval was extended to 12 weeks following pregnancy outcome. However, beyond this period and for the remainder of the first year after pregnancy outcome the mortality rate was virtually identical (RR = 1.01) to that observed in the referent group.

The exclusion of the 8 injury-related deaths does not affect the estimates of relative mortality risk across intervals but does reduce precision (Table 1). For example, the risk for mortality unrelated to injury for the period until 12 weeks after outcome was 2.12 (95% CI 0.96–4.66).

Of the deaths of women in the period including pregnancy and the 12 weeks following pregnancy outcome, 86% were disease-related. In the period including pregnancy and the 6 weeks following outcome, mortality was largely attributed to haemorrhage (n = 6), retained placenta (n = 4), obstetric shock (n = 1), obstructed labour (n = 2), eclampsia (n = 4), puerperal sepsis (n = 4) and tetanus (n = 1). Of the five disease-related deaths occurring in the 7–12 weeks postpartum, 4 were attributed to infection (1 sepsis, 1 respiratory infection, 1 leishmaniasis, 1 hepatitis). The fifth was an illness-related death for which a cause could not be assigned with confidence. Thereafter, 81% of all deaths were ascribed to disease, of which 15 (68.2%) were associated with infection (7 tuberculosis, 1 sepsis, 2 respiratory infection, 3 leishmaniasis, and 2 hepatitis).

### Discussion

Clearly, the time of greatest risk to women was from pregnancy outcome until 7 days later. In this period the mortality rate was 37 times higher than in the referent second-year period. From 2 to 6 weeks following pregnancy outcome the death rate was nearly five times higher than during the referent interval. Mortality in the late maternal period (7 to 52 weeks after pregnancy outcome) was 25% higher (Table 1), suggesting there to be only a modest elevation in risk beyond the conventional maternal period. However, the mortality rate of 848 deaths per 100 000 person-years and the RR of death of 2.59 during the second 6-week postpregnancy period were high and similar to the respective values of 726 deaths per 100 000 and 2.21 observed during the period including pregnancy and the subsequent 6 weeks. In contrast, as from 13 weeks and throughout the remainder of the first postpregnancy year, the

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<th>Table 1. Mortality rates of women during pregnancy and following pregnancy outcome in rural Nepal&lt;sup&gt;a&lt;/sup&gt;</th>
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<sup>a</sup> Based on pregnancy and postpartum person-time data for 6101 women, 7325 pregnancies and 78 deaths.

<sup>b</sup> The numbers of deaths by cause have changed slightly since the data were first published (8), as a result of further investigation and data cleaning.

RR = relative risk.

CI = confidence interval.
risk of maternal death did not differ (RR = 1.01) from the subsequent value. Thus the 25% elevation in mortality we observed during the late maternal period was entirely concentrated in the 7–12 weeks following pregnancy.

Our findings at first appear not to agree with those of a recent study in Senegal in which the all-cause pregnancy-related mortality rate (also calculated to cover the first 12 weeks following pregnancy) was reported to be similar to that of non-pregnant women aged 20–44 (7), and the rate of death attributable to non-obstetric causes was lower than that of non-pregnant women in this age group. This led the authors to conclude that women tended to experience a survival advantage during and shortly following pregnancy. In that study, however, the comparison group comprised the person-time for all women outside the defined pregnancy to 12 weeks post-outcome period, including that of unmarried and infertile women of the same age. In traditional societies it may be that women not fulfilling marital and childbearing roles have health or other problems that place them at an increased risk of death. Similarly, our preliminary analysis indicates that rural Nepalese women who failed to become pregnant during the three and a half years of observation died at a higher rate than women who became pregnant at least once during this period (West et al., unpublished data, 2001). Ronsmans and colleagues pointed out the potential influence of this selection bias, whereby comparatively healthy women were more able than others to conceive and bear children, on the interpretation of their findings in Senegal (7).

As in the Senegalese study, the pregnancy-related mortality estimates in our study incorporate deaths that were attributed to intentional and unintentional injury. There is evidence that such deaths could relate to pregnancy (12). Social pressures, reduced mobility and balance, and fatigue associated with pregnancy could predispose women to potentially fatal injury (2). Other studies have shown that pregnancy is a time of increased exposure of women to intentional injury or violence (12–15). In our study, women were 2.7 times more likely to suffer injury during the period of pregnancy and the 12 subsequent weeks than in the referent interval (Table 1).

The ICD-10 definition of pregnancy-related death (6) represents a practical measurement goal in developing countries where ascertaining the cause of death is often difficult, if not impossible. It is a classification that implicitly acknowledges a relationship between the state of pregnancy and the risk of death from non-obstetric illness and injury. However, the element of the ICD-10 definition relating to duration may be unsatisfactory. Evidence from our study suggests that the period of pregnancy-related mortality risk may extend to 12 weeks following pregnancy outcome. During this time there was a sustained increase in death from all causes. In rural settings in developing countries, expanding the period of risk to 12 weeks following pregnancy outcome may allow mortality related to pregnancy to be more fully ascertained and understood.

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Conflicts of interest: none declared.
**Resumen**

**Riesgo de defunción tras el embarazo en el Népal rural**

**Objetivo** Investigar durante cuánto tiempo presentaban las mujeres un mayor riesgo de defunción después del embarazo en el Népal rural.

**Métodos** Se realizó un análisis de datos prospectivos relativos a mujeres participantes en el grupo de control de un gran ensayo basado en la población. Se visitó semanalmente durante tres años a 14 805 mujeres de 14 a 45 años para registrar sus embarazos y mortalidad durante y después del embarazo, expresada en personas-tempo, fue comparada con la mortalidad de referencia no relacionada con el embarazo (> 52 semanas después del embarazo) en la misma cohorte.

**Resultados** El riesgo relativo de defunción durante el embarazo, excluido el comienzo del parto, fue de 0,93 (intervalo de confianza del 95%: 0,38-2,32). Durante el periodo perinatal, definido como el comprendido entre el comienzo de las contracciones y siete días después del desenlace clínico, el riesgo relativo de muerte fue de 37,02 (IC95%: 15,03-90,92). Los riesgos relativos para los períodos de 2 a 6 semanas, 7 a 12 semanas, y 13 a 52 semanas después del embarazo fueron de 4,82 (IC 95%: 1,77-13,07), 2,59 (IC 95%: 0,81-8,26) y 1,01 (IC 95%: 0,40-2,53), respectivamente. El riesgo relativo de defunción fue de 2,21 (IC95%: 1,03-4,71) durante el periodo considerado tradicionalmente para definir la mortalidad materna (embarazo más 6 semanas tras el desenlace clínico), y de 2,26 (IC95%: 1,05-4,90) cuando el periodo se extendió hasta 12 semanas después del desenlace del embarazo.

**Conclusion** El riesgo de defunción asociado al embarazo debería evaluarse durante las 12 semanas posteriores al desenlace clínico, en lugar de las 6 semanas habituales.

**References**