Iron and folic acid supplements and reduced early neonatal deaths in Indonesia

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Objective To examine the relationship between antenatal care, iron and folic acid supplementation and tetanus toxoid vaccination during pregnancy in Indonesia and the risk of early neonatal death (death in days 0–6 of life).
Methods We analysed pooled data on neonatal survival in singleton infants born in the 5 years before each of the Indonesian demographic and health surveys of 1994, 1997 and 2002–2003. Only the most recently born infant of each mother was included. Multivariate Cox proportional hazards models were used to identify factors linked to early neonatal death.
Findings Of the 40 576 infants included, 442 experienced early neonatal death. After adjustment, the risk of early neonatal death was significantly reduced for infants of mothers who received either any form of antenatal care (hazard ratio, HR: 0.48; 95% confidence interval, CI: 0.31–0.73), any quantity of iron and folic acid (HR: 0.53; 95% CI: 0.36–0.77) or ≥ 2 tetanus toxoid injections (HR: 0.66; 95% CI: 0.48–0.92). When we analysed different combinations of these measures, iron and folic acid supplementation provided the main protective effect: early neonatal deaths were still significantly reduced among infants whose mothers received iron and folic acid supplements but no other form of antenatal care (HR: 0.10; 95% CI: 0.01–0.67), or the supplements but < 2 tetanus toxoid injections (HR: 0.46; 95% CI: 0.29–0.73). Subsequent analysis showed that 20% of early neonatal deaths in Indonesia could be attributed to a lack of iron and folic acid supplementation during pregnancy.
Conclusion Iron and folic acid supplementation during pregnancy in Indonesia significantly reduced the risk of early neonatal death and could also do so in other low- and middle-income countries.

Une traduction en français de ce résumé figure à la fin de l'article. *Al final del artículo se facilita una traducción al español.* الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Globally, approximately 4 million infants die each year in the neonatal period, with 75% dying in the early neonatal period (i.e. in the first 7 days of life).[1,2] A recent review found that up to 70% of neonatal deaths worldwide could be averted by implementing universal (i.e. > 99%) coverage of 16 evidence-based interventions during the preconception, antenatal, intrapartum and postnatal periods.[3] The review showed that, at 90% coverage, the impact of intrapartum and postnatal packages of interventions on neonatal mortality was as much as three times greater than the impact of an antenatal care package. However, the provision of iron and folic acid supplements to pregnant women for preventing neonatal death was not considered.

A systematic review of eight trials comparing iron and folic acid supplementation and no treatment found only two studies that reported perinatal deaths.[4] Moreover, the sample sizes were too small for the results to be meaningful. In contrast, a recent large trial in China reported a 54% greater reduction in early neonatal mortality among neonates whose mothers received iron and folic acid supplements compared to those whose mothers received folic acid alone.[5] The lower mortality was associated with a significant reduction in the risk of early preterm delivery and with fewer deaths from birth asphyxia. These findings are consistent with trials in non-anaemic women in the United States of America (USA), which have demonstrated that the incidence of preterm birth is significantly lower in mothers who receive iron supplements.[6,7] Reports from developing countries also indicate that preterm delivery is the main contributor to neonatal death among low-birth-weight infants.[8,9] Providing iron and folic acid during pregnancy could decrease early neonatal mortality, possibly by reducing the risk of preterm birth and birth asphyxia.

In a previous analysis of the Indonesia demographic and health survey for 2002–2003, we confirmed that antenatal care and postnatal care services decreased neonatal mortality.[10] However, the effect of antenatal care alone and of its individual components could not be assessed because too few neonatal deaths were reported in this individual survey. The aim of this study, therefore, was to use data pooled from several surveys to determine whether the risk of early neonatal death is decreased in infants born to mothers who have received antenatal care in any form, iron and folic acid supplementation or tetanus toxoid vaccination.

Methods

Data sources

Since 1982, Indonesian demographic and health surveys have collected demographic data and information on the health status of nationally representative population samples approximately every 5 years. The sampling methods have been reported elsewhere.[11,12]

The data used in the present study were derived from the 1994, 1997 and 2002–2003 surveys. In total, information on 86 461 women was obtained from these surveys: 29 483 from the 1994 survey, 28 810 from the 1997 survey and 28 168 from

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the 2002–2003 survey. On average, the response rate was over 97.5%.[11,13,14] In addition, information was also available on the survival of 40 576 singleton infants who were the most recent born to ever-married women in the 5 years before each survey. The most recent births were selected because health service information was available on these births only and because the mothers' recollections were less likely to be affected by recall bias.

Study outcome and variables

The primary study outcome was early neonatal death, which was defined as the death of a newly born infant during the first week of life (i.e. during days 0–6).[2] The information was obtained on interviewing ever-married women taking part in the survey.

The main exposure variable investigated was antenatal care, which was defined as any health-care service provided by trained health personnel during pregnancy. Antenatal care might include physical examinations, health education, iron and folic acid supplementation and tetanus toxoid vaccination. To assess the effect of iron and folic acid supplementation and tetanus toxoid vaccination individually, we analysed the way in which different combinations of any form of antenatal care, iron and folic acid supplementation and tetanus toxoid vaccination influenced early neonatal mortality.

In evaluating other factors associated with early neonatal death, we adapted the analytical framework developed by Mosley & Chen[15] to suit the available information. Two main groups of variables were identified: (i) community and socioeconomic status characteristics, such as paternal schooling, housing and wealth, and (ii) proximate determinants (or intermediate variables), such as maternal age, birth rank and pregnancy complications. In addition, the effects of skilled attendance at delivery and mode and place of delivery were also examined.

A household wealth index was constructed by assigning weights to three housing characteristics (i.e. availability of electricity and type of floor and wall) and six household assets (i.e. possession of a radio, television, fridge, bicycle, motorcycle and car) using the survey data and principle components analysis.[16] The wealth index was used to rank all households across the three surveys.

The mother's subjective assessment of her infant's size at birth (i.e. smaller than average, average or larger than average) was used as a birth weight indicator because 36% of infants had not been weighed at birth.

Statistical analysis

The characteristics of the study population were described using frequency tabulations. The crude hazard ratios (HRs) for factors associated with early neonatal death were determined by bivariate analysis, performed using a Cox proportional hazards regression model. In addition, multivariate analysis was used to examine the independent effect of each variable after controlling for covariates.

First, backward elimination was used to remove non-significant factors among community and socioeconomic variables, using a significance level of 0.05. However, two variables were retained in the final model regardless of their level of significance: the year of the survey and maternal age at child birth.[17] Second, four pregnancy and delivery health-care services were assessed after controlling for significant community and socioeconomic variables: antenatal care, mode of delivery, place of delivery and skilled attendance at delivery. Only significant variables were retained in the model, apart from skilled attendance at delivery, which was retained because it is known to have a protective effect.[2] Since antenatal care was highly correlated with both iron and folic acid supplementation and tetanus toxoid vaccination, the antenatal care variable was replaced by these other two variables in the final model. Subsequently, the effect on early neonatal mortality of the combination of any form of antenatal care and iron and folic acid supplementation and the combination of iron and folic acid supplementation and tetanus toxoid vaccination was examined. The HR and 95% confidence interval (CI) for early neonatal death were determined for each factor.

A similar modelling strategy, involving multivariate logistic regression, was used to assess the association between iron and folic acid supplementation and birth weight.

All statistical analyses were performed using STATA/MP version 10.00 (Stata Corporation, College Station, USA) and Cox proportional hazards models were fitted using STATA survey commands to adjust for sampling weights and the cluster survey design. Sampling weights were applied to compensate for the sampling design or sampling errors. The primary sampling unit was a cluster of census blocks of 25 selected households.

The population attributable risk (PAR) of early neonatal death in women in the general population who did not receive iron and folic acid supplements during pregnancy (w) was calculated using the formula:[18–20]

$$\mathrm{PAR} = w \times \frac{(\mathrm{aHR} - 1)}{\mathrm{aHR}} \qquad (1)$$

where aHR is the adjusted HR for early neonatal death in neonates born to women who did not take iron and folic acid supplements during pregnancy. This aHR is the inverse of the value reported for women who did take iron and folic acid supplements. Women who reported not knowing if they had taken iron and folic acid supplements were assumed not to have taken them.

Results

Of the 40 576 live-born singleton infants most recently born to each mother in the 5 years before each survey interview date, 442 experienced early neonatal death. They included 168 of the 13 727 infants in the 1994 survey (rate: 12.2 per 1000), 146 of the 13 609 in the 1997 survey (rate: 10.7 per 1000) and 128 of the 13 240 in the 2002–2003 survey (rate: 9.7 per 1000). In 1994, 70% of all neonatal deaths occurred in the early neonatal period; the proportion increased to 74% in 1997 and then to 78% in 2002–2003.

Table 1 gives details of the provision of different pregnancy and delivery health-care services reported in the three surveys. Overall there was a progressive increase in the prevalence of antenatal care, and 72% of mothers received iron and folic acid supplementation in the last survey.

The results of a multivariate analysis of how community and socioeconomic variables influenced the risk of early neonatal death are shown in Table 2. The risk was significantly increased in infants who were smaller than average, infants born to mothers who experienced delivery complications, infants who were reportedly born early and male infants. There was a greatly increased risk of early neonatal death in infants who were reportedly both smaller than average and born early. When the variable birth

Table 1. **The prevalence of pregnancy and delivery health-care services provided to mothers of singleton infants interviewed in three demographic and health surveys in Indonesia, 1994–2003**

Pregnancy or delivery health-care service	Interviewed		Percentage of weighted total[b]	Weighted prevalence[b] (%)		
	No.[a]	Weighted No.[b]		1994 survey	1997 survey	2002–2003 survey
ANC[c]						
No ANC	5306	4211	10.8	15.4	8.9	8.0
Any ANC	34924	34533	88.6	84.2	90.5	91.2
IFA supplements						
None	9595	8253	21.2	26.4	16.9	20.1
< 90 tablets	19437	18972	48.7	52.7	49.9	43.2
≥ 90 tablets	8061	8763	22.5	14.4	24.3	29.1
Unknown	3171	2746	7.0	6.4	8.9	5.8
TT vaccination						
None	11622	10695	27.4	31.2	24.8	26.2
1 injection	7615	7366	18.9	17.0	18.4	21.4
≥ 2 injections	20745	20297	52.1	50.7	54.8	50.7
Mode of delivery						
Not Caesarean section	39104	37515	96.3	97.4	95.4	96.0
Caesarean section	1472	1457	3.7	2.6	4.6	4.0
Place of delivery						
Not in a health-care facility	29819	28683	73.6	82.2	79.0	59.0
In a health-care facility	10690	10240	26.3	17.6	21.0	40.8
Skilled attendance at delivery						
None or untrained delivery attendant	18342	18526	47.5	59.5	50.0	32.5
Trained delivery attendant	22185	20414	52.4	40.5	50.1	67.3

ANC, antenatal care; IFA, iron and folic acid; TT, tetanus toxoid.
[a] The total number varies between categories because some values are missing.
[b] Weighting was applied to compensate for the sampling design or sampling errors.
[c] Antenatal care may or may not include iron and folic acid supplementation and tetanus toxoid vaccination.

size was replaced by birth weight, similar results were observed.

Of the four pregnancy and delivery health-care services considered (i.e. mode of delivery, place of delivery, skilled attendance at delivery and antenatal care), only antenatal care demonstrated a significant protective effect against early neonatal death after adjusting for all significant community and socioeconomic characteristics as well as skilled attendance at delivery. On replacing antenatal care in the analytical model with either any quantity of iron and folic acid supplementation or tetanus toxoid vaccination during pregnancy, we found that the adjusted risk of early neonatal death was reduced by 34% in infants born to mothers who received two or more tetanus toxoid injections and by 47% in those born to mothers who received iron and folic acid supplementation (Fig. 1). The risk of early neonatal death was reduced by 44% (adjusted HR: 0.56; 95% CI: 0.35–0.89) for mothers taking less than 30 iron and folic acid supplement tablets during pregnancy, by 50% (adjusted HR: 0.50; 95% CI: 0.31–0.79) for those taking 30–89 tablets, by 53% (adjusted HR: 0.47; 95% CI: 0.26–0.85) for those taking 90–119 tablets, and by 44% (adjusted HR: 0.56; 95% CI: 0.29–1.08) for those taking 120 or more tablets. The magnitude of the protective effect of iron and folic acid supplementation progressively decreased over time, from a 57% reduction (adjusted HR: 0.43; 95% CI: 0.23–0.79) in the 1994 survey to a 39% reduction (adjusted HR: 0.61; 95% CI: 0.35–1.09) in the 1997 survey and a 36% reduction (adjusted HR: 0.64; 95% CI: 0.20–2.06) in 2002–2003 survey.

Multivariate analysis of the effect of different combinations of any form of antenatal care, iron and folic acid supplementation and tetanus toxoid vaccination showed that iron and folic acid supplementation was responsible for the main protective effect against early neonatal death. Table 3 shows that the infants of mothers who received ≥ 2 tetanus toxoid injections but no iron and folic acid supplementation were not significantly protected against early neonatal death, while infants whose mothers had received iron and folic acid supplementation but < 2 tetanus toxoid injections were. When we examined only combinations of iron and folic acid supplementation and antenatal care (Table 3), we found that the risk of early neonatal death was significantly lower in infants born to women who received iron and folic acid supplementation (i.e. independently from a traditional birth attendant or by purchasing it themselves) but did not receive antenatal care in any other form than in those born to women who received neither. Although there was only a borderline significant reduction in risk in infants of women who received antenatal care that did not include iron and folic acid supplementation, the risk reduction was significant in those whose antenatal care did include iron and folic acid supplementation.

Analysis of the relationship between iron and folic acid supplementation and size at birth showed that the likelihood of having a smaller than average infant was 19% lower among mothers who reported using iron and folic acid supplements

Table 2. **Hazard ratios for early neonatal mortality for community and socioeconomic status variables, as determined by multivariate analysis, Indonesia, 1994–2003**

Variable	*n*[a]	%	Unadjusted[a,b]		Adjusted[a,b]	
			HR	95% CI	HR	95% CI
Survey year						
1994	13282	34.1	1.00	Reference	1.00	Reference
1997	13043	33.5	0.90	0.64–1.27	0.88	0.62–1.25
2002–2003	12646	32.5	0.69	0.45–1.05	0.72	0.46–1.13
Community and socioeconomic variables						
Region and area of residence						
Java–Bali region, urban	9120	23.4	1.00	Reference	1.00	Reference
Java–Bali region, rural	14027	36.0	1.16	0.70–1.90	NS	NS
Sumatera region, urban	2296	5.9	1.30	0.72–2.33	NS	NS
Sumatera region, rural	6146	15.8	0.96	0.59–1.56	NS	NS
Eastern Indonesia region, urban	1801	4.6	1.03	0.58–1.81	NS	NS
Eastern Indonesia region, rural	5581	14.3	1.41	0.90–2.22	NS	NS
Average duration of paternal schooling[c] (years)	Mean (SE): 7.32 (0.07)		0.94	0.89–0.99	NS	NS
Maternal education						
None	3218	8.3	1.00	Reference	1.00	Reference
Primary not completed	9071	23.3	0.80	0.44–1.44	0.82	0.46–1.46
Primary completed	12734	32.7	0.74	0.42–1.32	0.81	0.45–1.46
Secondary not completed	6437	16.5	0.61	0.34–1.10	0.68	0.37–1.24
Secondary completed	5924	15.2	0.63	0.32–1.22	0.66	0.33–1.34
Tertiary	1588	4.1	0.36	0.13–0.98	0.31	0.12–0.83
Maternal marital status						
Currently married	37944	97.4	1.00	Reference	1.00	Reference
Formerly married	1028	2.6	1.65	0.75–3.62	NS	NS
Parental occupation						
Non-working mother and working father	21866	56.1	1.00	Reference	1.00	Reference
Working mother and working father	16232	41.7	1.37	1.00–1.88	NS	NS
Unemployed father	722	1.9	1.49	0.44–5.04	NS	NS
Household wealth index	Mean (SE): 0.20 (0.03)		0.92	0.84–1.01	NS	NS
Proximate determinants						
Maternal age at childbirth, in years	Mean (SE): 26.8 (0.06)		1.01	0.99–1.04	1.02	0.99–1.04
Sex of child						
Female	18875	48.4	1.00	Reference	1.00	Reference
Male	20097	51.6	1.57	1.14–2.16	1.66	1.19–2.32
Birth rank and interval						
Second or third child, interval > 2 years	14101	36.2	1.00	Reference	1.00	Reference
First child	12197	31.3	1.14	0.74–1.76	NS	NS
Second or third child, interval ≤ 2 years	2556	6.6	1.23	0.68–2.23	NS	NS
Fourth or higher child, interval > 2 years	8562	22.0	1.24	0.81–1.90	NS	NS
Fourth or higher child, interval ≤ 2 years	1555	4.0	1.52	0.87–2.64	NS	NS
Desire for pregnancy						
Wanted at the time	32082	82.3	1.00	Reference	1.00	Reference
Wanted later	3542	9.1	1.20	0.65–2.20	NS	NS
Unwanted	3286	8.4	0.99	0.57–1.72	NS	NS
Delivery complications						
No	27178	69.7	1.00	Reference	1.00	Reference
Yes	11584	29.7	1.93	1.40–2.65	1.80	1.28–2.53
Reported birth size and timing of delivery						
Average size and born on time	19421	49.8	1.00	Reference	1.00	Reference
Average size and born early	286	0.7	7.33	3.08–17.41	7.69	3.17–18.67
Smaller than average and born on time	4738	12.2	2.41	1.60–3.62	2.34	1.55–3.53
Smaller than average and born early	417	1.1	16.64	10.46–26.47	15.22	9.32–24.85
Larger than average	13118	33.7	1.06	0.69–1.64	1.00	0.64–1.57

CI, confidence interval; HR, hazard ratio; NS, not significant; SE, standard error.

[a] Weighting was applied to compensate for the sampling design or sampling errors.

[b] Data on 2574 cases were missing and they were excluded from the analysis.

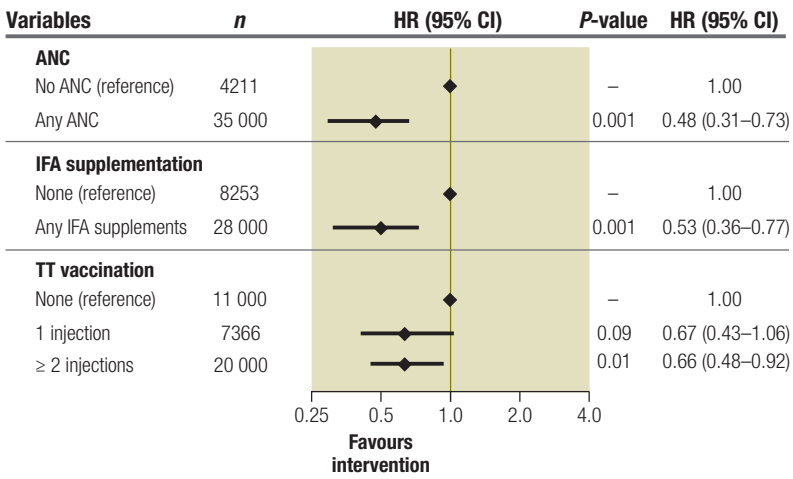
[c] Paternal schooling in the clusters; clusters were the primary sampling units comprising census blocks of 25 selected households.

(adjusted odds ratio, OR: 0.81; 95% CI: 0.72–0.91) than among those who did not. A small dose–response effect was apparent: the likelihood of having a smaller than average infant was 18% lower (adjusted OR: 0.82; 95% CI: 0.72–0.93) for mothers who reported taking < 90 iron and folic acid tablets and 22% lower (adjusted OR: 0.78; 95% CI: 0.66–0.92) for those who took ≥ 90 tablets. Findings were similar when birth weight was considered instead (data not shown).

We also found that iron and folic acid supplementation and tetanus toxoid vaccination had a protective effect against death during the entire neonatal period (i.e. within the first 30 days of life). The risk of death was significantly lower for neonates born to mothers who reported receiving iron and folic acid supplementation (adjusted HR: 0.60; 95% CI: 0.43–0.84) or ≥ 2 tetanus toxoid injections during pregnancy (adjusted HR: 0.72; 95% CI: 0.53–0.97).

On the assumption that the association between iron and folic acid supplementation and early neonatal death in the pooled data was causal, we calculated that 20% of early neonatal mortality in Indonesia could be attributed to a lack of iron and folic acid supplementation during pregnancy (PAR: 0.20; 95% CI: 0.08–0.32). Moreover, there was a progressive decrease in the PAR across the surveys: from 30% (PAR: 0.30; 95% CI: 0.09–0.49) in 1994 to 11% (PAR: 0.11; 95% CI: −0.23–0.38) in 2002–2003.

Fig. 1. **Effects of antenatal care,[a] iron and folic acid supplementation and tetanus toxoid vaccination during pregnancy on early neonatal mortality, Indonesia, 1994–2003**



ANC, antenatal care; CI, confidence interval; HR, hazard ratio; IFA, iron and folic acid; TT, tetanus toxoid.
[a] Antenatal care may or may not include iron and folic acid supplementation and tetanus toxoid vaccination.

Discussion

We found that the risk of early neonatal death in Indonesia was reduced by the provision of any form of antenatal care. Moreover, viewed individually, two components of antenatal care, namely iron and folic acid supplementation and tetanus toxoid vaccination, also reduced the risk. The main protective effect came from iron and folic acid supplementation. Infants were not significantly protected against early neonatal death when mothers received antenatal care or tetanus toxoid vaccination without iron and folic acid supplementation. In contrast, the risk of early neonatal death was significantly lower in the infants of mothers who used any quantity of iron and folic acid supplements during pregnancy irrespective of the other services received. These findings are consistent with those of a recently reported trial of micronutrient supplementation during pregnancy in rural China, which found a 54% greater reduction in early neonatal death in infants whose mothers had received standard iron and folic acid supplementation than in those whose mothers had received folic acid alone.[5]

Table 3. **The effect of different combinations of iron and folic acid supplementation, tetanus toxoid vaccination and antenatal care on early neonatal mortality, as determined by multivariate analysis, Indonesia, 1994–2003**

Variable	n[a]	%[a]	Unadjusted[b]		Adjusted[b,c]	
			HR	95% CI	HR	95% CI
Combination of IFA supplementation and TT vaccination						
No IFA supplements with < 2 TT injections	6 713	17.2	1.00	Reference	1.00	Reference
No IFA supplements with ≥ 2 TT injections	1 389	3.6	0.61	0.27–1.38	0.64	0.28–1.46
IFA supplements with < 2 TT injections	10 161	26.1	0.44	0.28–0.69	0.46	0.29–0.73
IFA supplements with ≥ 2 TT injections	17 298	44.4	0.45	0.30–0.66	0.49	0.32–0.74
Combination of ANC and IFA supplementation						
No ANC and no IFA supplements	3 862	9.9	1.00	Reference	1.00	Reference
ANC without IFA supplements	4 309	11.1	0.58	0.34–1.00	0.60	0.35–1.04
IFA supplements alone[d]	294	0.80	0.09	0.01–0.68	0.10	0.01–0.67
ANC including IFA supplements	27 408	70.3	0.38	0.25–0.57	0.41	0.26–0.64

ANC, antenatal care; CI, confidence interval; HR, hazard ratio; IFA, iron and folic acid; TT, tetanus toxoid.
[a] Weighting was applied to compensate for the sampling design or sampling errors.
[b] Data on 2574 cases were missing and they were excluded from the analysis.
[c] Adjusted for reported birth size, timing of delivery, delivery complications, child's sex, maternal education, maternal age at childbirth, skilled attendance at delivery and year of survey.
[d] Women may have obtained IFA supplements outside of ANC services from a traditional birth attendant or by purchasing it themselves.

This is the first time an association between iron and folic acid supplementation in pregnancy and a reduced risk of neonatal death has been reported with national data. The protective influence of iron and folic acid supplementation observed in Indonesia might also be important for pregnant women in other low- and middle-income countries.[21] We estimated that in Indonesia, where 72% of pregnant women reported using iron and folic acid supplementation,[22] 20% of neonatal deaths could be attributed to mothers not using these supplements.

The progressive decrease in the magnitude of the protective effect of iron and folic acid supplementation on early neonatal death observed in the Indonesian surveys might be attributable to improvements in the iron status of pregnant women over time.

Previous reviews of interventions that may be effective in reducing neonatal mortality have not considered iron and folic acid supplementation.[3] Combined with the results of the Chinese trial mentioned above,[5] our findings indicate that antenatal care should include the promotion and supply of iron and folic acid supplementation for pregnant women as a key intervention.

Biological mechanisms

Previous reports indicate that there may be a relationship between the use of iron and folic acid supplements in pregnancy and a reduction in preterm delivery as well as an increase in infant birth weight.[5] Studies in developing countries have reported that preterm delivery is one of the main contributors to neonatal mortality, including early neonatal death.[8,9] Although global estimates of neonatal mortality in 2005 indicate that 27% of neonatal deaths were due to preterm delivery,[1] a review of all stillbirths and early neonatal deaths in seven centres participating in a World Health Organization (WHO) multicentre calcium supplementation trial for the prevention of pre-eclampsia found that prematurity accounted for 62% of early neonatal mortality.[9] Similarly, a cohort study of low-birth-weight neonates in Bangladesh reported that 75% of neonatal deaths could be attributed to preterm delivery.[8]

In this study, we were able to demonstrate that significantly fewer infants born to mothers who received iron and folic acid supplementation were smaller than average, which suggests that a decrease in the risk of an infant having a low birth weight may be the mechanism responsible for reduced early neonatal mortality.

Neonatal survival

Using the population estimate for Indonesia from the 2005 Intercensal Population Survey[23] and the PAR calculated in our study, we estimate that almost 15 000 early neonatal deaths could be averted each year in the country by providing universal iron and folic acid supplementation to pregnant women. In Indonesia, it is recommended that pregnant women take 60 mg of iron and 0.25 mg of folic acid every day in the second trimester (i.e. 90 tablets). The supplements are distributed through a variety of health services, including health centres, village health posts, village drug posts, village midwives and traditional birth attendants.[24] Although in 2005 the coverage of iron and folic acid supplementation during pregnancy was relatively high in the country, it varied widely by province.[22] An assessment of the cost-effectiveness of universal iron and folic acid supplementation in pregnant women for preventing early neonatal death is needed. However, it is likely that universal iron and folic acid supplementation would be cost-effective since Indonesia has already invested in a national programme for distributing supplements through village midwives, primary health-care centres and village health posts.

Multiple micronutrient supplements

A trial in Indonesia that compared the effect of multiple micronutrient supplements and iron and folic acid supplements on fetal loss and infant deaths reported that the rate of early infant mortality in the first 0–90 days was 18% lower in pregnant women who received multiple micronutrient supplements than in those who received iron and folic acid supplements only.[25] However, only 30 mg of iron were administered in both treatment arms and no significant difference in neonatal mortality was observed.

Other perinatal services

The number of neonatal deaths due to neonatal tetanus has halved since 1990 and currently only 7% of neonatal deaths worldwide are due to neonatal tetanus.[1] A study in Bangladesh found that a substantial decrease in neonatal mortality was partly due to less neonatal tetanus.[26] In our study, the lower protective effect of tetanus toxoid vaccination compared with iron and folic acid supplementation against early neonatal death may have been due to the rapid decline in neonatal tetanus that occurred between the three surveys.[27] Since the early 1990s, routine tetanus toxoid immunization has been provided in Indonesia for pregnant women and women getting married, with supplementary vaccinations being given to those aged 15–39 years living in high-risk areas for neonatal tetanus.[27] Unfortunately, we could not explore the changing effect of tetanus toxoid vaccination across the surveys because of limited sample sizes.

In practice, antenatal care provides an opportunity for pregnancy-related complications to be detected and for education about healthy lifestyles that will benefit both mother and infant. In 2005, 77% of pregnant women in Indonesia overall received four or more antenatal care checks, though only 45% received them in Papua province.[22] There is, therefore, scope to expand antenatal care services, including increasing iron and folic acid supplementation for pregnant women. Moreover, the factors found to be significantly associated with early neonatal mortality were similar to those we have previously reported as being associated with general neonatal mortality in Indonesia.[10]

Strengths and limitations

The study was based on nationally representative surveys conducted over a 9-year period and involving large samples. These surveys all used the same core questionnaire, were implemented by the same organizations and employed consistent quality control methods.[11,13,14] The validity of the analysis was further enhanced by restricting the data analysed to reports of each mother's most recent birth in the 5 years preceding each survey, to minimize recall bias.[28–30] Finally, the substantial sample sizes made it possible to analyse the effects of different health-care service factors, such as antenatal care services in general, iron and folic acid supplementation and tetanus toxoid vaccination, and combinations of these factors, while controlling for a range of other variables known to be associated with neonatal mortality.

One limitation is that the information provided by respondents could not be validated. However, child mortality, in-

cluding neonatal mortality, is a core measure in demographic and health surveys and the survey methods used have been carefully examined over many years.[31] Underreporting of neonatal deaths can occur but, in general, it is less likely for events in the recent past. Usage of iron and folic acid supplementation during pregnancy was based on the women's recall and any improvement in iron status could not be assessed. Similarly, we were unable to determine whether the risk of preterm birth or birth asphyxia was reduced in the infants of women who took iron and folic acid supplements. It is also possible that the neonatal mortality rate was underestimated because birth histories and infant survival data were collected from surviving women only.[28] Furthermore, we could not investigate the effect of variables that had not been recorded in all three surveys. In particular, we could not determine whether malaria infection or prophylaxis during pregnancy modified the effect of iron and folic acid supplementation on neonatal mortality because the relevant information was not collected.[32] Nonetheless, these limitations are unlikely to have substantially influenced the validity of the analyses of the pregnancy care services examined or their association with neonatal survival.

Conclusion

We found that iron and folic acid supplementation had a strong protective effect against early neonatal death and that some 20% of early neonatal mortality could be averted in Indonesia by universal iron and folic acid supplementation during pregnancy. The use of iron and folic acid supplementation during pregnancy should be included in future neonatal care packages aimed at reducing neonatal mortality. ■

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الملخص

تعزيزات الحديد وحمض الفوليك والحد من وفيات الولدان المبكرة في اندونيسيا

الهدف فحص العلاقة بين الرعاية السابقة للولادة، وتعزيز الحديد وحمض الفوليك والتطعيم بذوفان الكزاز(التتانوس) أثناء الحمل في اندونيسيا وخطر الوفاة المبكرة للولدان (الوفاة خلال الأيام الستة الأولى من العمر).

الطريقة حلل الباحثون، في الخمس سنوات السابقة، المعطيات التجميعية لبقاء الولدان المولودين ولادة مفردة على قيد الحياة لكل من المسوح الصحية الديموغرافية الاندونيسية التي أجريت في الأعوام 1994، 1997، 2002-2003. وأدرج في البحث فقط أحدث مولود لكل أم. واستخدمت نماذج كوكس عديدة المتغيرات للمخاطر لتحديد العوامل المرتبطة بوفيات الولدان المبكرة.

الموجودات من بين 40576 مولوداً مدرجاً في الدراسة، تعرض 442 مولوداً لوفاة مبكرة. وبعد إجراء التصحيحات، تبين أن خطر وفاة الولدان المبكرة قد انخفض انخفاضاً ملموساً بالنسبة لمواليد الأمهات سواء اللاتي تلقين أي شكل من أشكال الرعاية السابقة للولادة (نسبة المخاطرة: 0.48؛ فاصل ثقة 95%: 0.31 – 0.73)، أو اللاتي تناولن أي كمية من الحديد وحمض الفوليك (نسبة المخاطرة: 0.53؛ فاصل ثقة 95%: 0.36 – 0.77) أو جرى حقنهن بجرعتين أو أكثر من ذوفان الكزاز (نسبة المخاطرة 0.66؛ فاصل ثقة 95% 0.48 – 0.92). وعندما حلل الباحثون التركيبات المختلفة لهذه التدابير، تبين أن تعزيز الحديد وحمض الفوليك أتاح التأثير الوقائي الأساسي: فقد استمر انخفاض وفيات الولدان المبكرة انخفاضاً ملموساً بين المواليد الذين تلقت أمهاتهم تعزيزات من الحديد وحمض الفوليك ولم يحصلن على أي نوع آخر من الرعاية السابقة للولادة (نسبة المخاطرة: 0.10؛ فاصل ثقة 95%: 0.01 – 0.67). أو تلقت التعزيزات مع أقل من جرعتين من ذوفان الكزاز (نسبة المخاطرة: 0.46؛ فاصل ثقة 95%: 0.29 – 0.73). وأظهرت التحليلات التالية أن 20% من وفيات الولدان المبكرة في اندونيسيا يمكن أن تعزى إلى نقص تعزيز الحديد وحمض الفوليك أثناء الحمل.

الاستنتاج تعزيز الحديد وحمض الفوليك أثناء الحمل في اندونيسيا يؤدي إلى خفض ملموس في خطورة وفيات الولدان المبكرة ويمكن أن يؤدي أيضاً إلى ذلك في البلدان المنخفضة والمتوسطة الدخل.

Résumé

Supplémentation en fer et en acide folique et réduction de la mortalité néonatale précoce en Indonésie

Objectif Examiner la relation entre soins anténatals, supplémentation en fer et en acide folique et vaccination par l'anatoxine tétanique pendant la grossesse d'une part et risque de décès néonatal précoce (intervenant entre 0 et 6 jours de vie) d'autre part, en Indonésie.

Méthodes Nous avons analysé des données combinées sur la survie des nouveau-nés, issus d'une grossesse monofoetale dans les 5 ans précédant chacune des enquêtes démographiques et sanitaires menées en Indonésie en 1994, 1997 et 2002-2003. Seul le dernier né des enfants de chaque mère avait été inclus dans l'étude. Nous avons utilisé des modèles multivariés à risque proportionnel de Cox pour identifier les facteurs liés à la mortalité néonatale précoce.

Résultats Parmi les 40 576 enfants pris en compte, 442 sont décédés avant l'âge de 7 jours. Après ajustement, le risque de décès néonatal précoce apparaissait significativement réduit pour les enfants dont les mères avaient reçu une forme quelconque de soins anténatals (rapport de risques, RR : 0,48 ; intervalle de confiance à 95 % : 0,31-0,73), du fer et de l'acide folique en une quantité quelconque (RR : 0,53 ; IC à 95 % : 0,36-0,77) ou 2 injections et plus d'anatoxine tétanique (RR : 0,66 ; IC à 95 % : 0,48-0,92). L'analyse de différentes combinaisons de ces mesures montre que c'est la supplémentation en fer et en acide folique qui fournit l'effet protecteur le plus important La mortalité néonatale précoce était encore significativement réduite chez les nourrissons dont les mères avaient reçu une telle supplémentation en l'absence d'autre forme de soins anténatals (RR : 0,10 ; IC à 95 % : 0,01-0,67) ou cette supplémentation et moins de 2 injections d'anatoxine tétanique (RR : 0,46 ; IC à 95 % : 0,29-0,73). L'analyse réalisée à la suite a mis en évidence que 20 % des décès néonatals précoces survenant en Indonésie pourraient être attribués à l'absence de supplémentation en fer et en acide folique pendant la grossesse.

Conclusion En Indonésie, l'apport d'une supplémentation en fer et en acide folique pendant la grossesse a réduit significativement le risque de décès néonatal précoce et pourrait en faire autant dans d'autres pays à revenu faible ou intermédiaire.

Resumen

Suplementos de hierro y ácido fólico y reducción de la mortalidad neonatal precoz en Indonesia

Objetivo Estudiar en Indonesia la relación existente entre, por un lado, la atención prenatal, los suplementos de hierro y ácido fólico y la vacunación con anatoxina tetánica durante el embarazo y, por el otro, el riesgo de muerte neonatal precoz (defunción dentro de los primeros 6 días de vida).

Métodos Analizamos datos combinados sobre la supervivencia neonatal de lactantes nacidos de embarazos monofetales en los 5 años anteriores a cada una de las encuestas de demografía y salud de Indonesia de 1994, 1997 y 2002–2003. Solo se incluyó en el estudio al lactante de menor edad de cada madre. Para determinar los factores relacionados con la muerte neonatal precoz se aplicaron modelos multifactoriales de riesgos proporcionales de Cox.

Resultados De los 40 576 lactantes estudiados, 442 fallecieron tempranamente en el periodo neonatal. Tras ajustar las cifras, el riesgo de muerte neonatal precoz se redujo de manera significativa cuando las madres habían recibido cualquier tipo de atención prenatal (razón de riesgos instantáneos (*hazard ratio*, HR): 0,48; intervalo de confianza del 95%: 0,31–0,73), cualquier cantidad de hierro y ácido fólico (HR: 0,53, IC95%: 0,36–0,77) o ≥2 inyecciones de anatoxina tetánica (HR: 0,66; IC95%: 0,48–0,92). Cuando analizamos las diferentes combinaciones de esas medidas, observamos que los suplementos de hierro y ácido fólico tenían el mayor efecto protector: la mortalidad neonatal precoz seguía siendo considerablemente inferior entre los lactantes cuyas madres habían recibido suplementos de hierro y ácido fólico, pero ninguna otra forma de atención prenatal (HR: 0,10; IC95%: 0,01–0,67), o bien los suplementos pero menos de 2 inyecciones de anatoxina tetánica (HR: 0,46, IC95%: 0,29–0,73). Análisis posteriores mostraron que el 20% de la mortalidad neonatal precoz registrada en Indonesia podía atribuirse a la falta de suplementos de hierro y ácido fólico durante el embarazo.

Conclusión La administración de suplementos de hierro y ácido fólico durante el embarazo redujo significativamente el riesgo de muerte neonatal precoz en Indonesia, y la medida podría tener el mismo efecto en otros países de ingresos bajos y medios.

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