Recurrence of adverse perinatal outcomes in developing countries

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Objective To evaluate the risk of recurrence of adverse perinatal outcomes in second pregnancies in developing countries.

Methods Data from the 2004–2008 Global Survey on Maternal and Perinatal Health were used to determine the outcomes of singleton second pregnancies for 61 780 women in 23 developing countries. The mother–infant pairs had been followed up until discharge or for 7 days postpartum.

Findings At the end of their second pregnancies, women whose first pregnancy had ended in stillbirth ($n = 1261$) or been followed by neonatal death ($n = 1052$) were more likely than women who had not experienced either outcome to have given birth to a child with a birth weight of < 1500 g (odds ratio, OR: 2.52 and 2.78, respectively) or 1500–2499 g (OR: 1.22 and 1.60, respectively), or to an infant requiring admission to an intensive care unit (OR: 1.64 and 1.68, respectively). At the end of their second pregnancies, those whose first pregnancy had ended in a stillbirth were at increased risk of another stillbirth (OR: 2.35) and those whose first infant had died as a neonate were at increased risk of having the second infant die within the first 7 days of life (OR: 2.82). These trends were found to be largely unaffected by the continent in which the women lived.

Conclusion In the developing world, a woman whose first pregnancy ends in stillbirth or is followed by the death of the neonate is at increased risk of experiencing the same outcomes in her second pregnancy.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Although stillbirths and neonatal deaths are tragic events to the affected mothers and their families, they remain common pregnancy outcomes in developing countries.[1–3] Almost all (97–99%) of the estimated 3 to 4 million stillbirths and 3 million neonatal deaths that occur each year globally occur in low- and middle-income countries.[3,4] The causes of stillbirth and neonatal death are generally inseparable.[5] The main risk factors for stillbirth include intrapartum complications, maternal infection in pregnancy, maternal disorders (such as hypertension and diabetes), fetal growth restriction and congenital abnormalities.[1] The additional risk factors for neonatal death include preterm birth, low birth weight, intrapartum complications and neonatal infection.[3,6]

Although the women who have suffered stillbirths or seen their neonates die often still want children, they are naturally anxious about the recurrence of adverse outcomes during or after subsequent pregnancies. Most of the data available on the recurrence of perinatal deaths have come from a few developed countries that have efficient systems for the registration of perinatal deaths, and the data on the recurrence of stillbirth appear to be inconsistent.[7,8] Very little is known about the risks of such recurrence in developing countries, partly because the recording of perinatal deaths in such countries – which often have no reliable maternity and neonatal databank linked to unique personal identification numbers – is generally poor and difficult.[2,9,10] The main aim of the present study is to fill this knowledge gap by examining the associations between adverse outcomes in the first and second pregnancies among women in developing countries. The study of recurrence risk can help identify the causes of adverse pregnancy outcomes – including, possibly, intrinsic and unavoidable risk factors relating to the mother – and guide the counselling of women of childbearing age.[10]

We used survey data collected in 23 developing countries in Africa, Asia and Latin America as part of the Global Survey on Maternal and Prenatal Health of the World Health Organization (WHO). Our main aim was to examine how – and if – stillbirth or neonatal death in the first pregnancy of a woman in a developing country affected the risk of stillbirth, early neonatal death, admission of the infant to a neonatal intensive care unit (ICU), having a low-birth-weight child and/or the preterm delivery of a child that was small for gestational age in that woman's second pregnancy. A secondary aim was to see if any associations that we detected differed according to the continent in which the woman lived. Since parity has an effect on pregnancy outcome,[11] we analysed only the data for women whose second pregnancies and deliveries were included in the Global Survey.

Methods

Study population

The study population and data collection methods used in this survey are described elsewhere.[12,13] The data analysed came from the 2004–2008 Global Survey (the data were collected in 2004–2005 in Africa and Latin America and in 2007–2008 in Asia). The Global Survey, which was multinational and facility-based, was originally designed to help develop a system for monitoring maternal and perinatal health worldwide.[12] Stratified multistage cluster sampling was used to select study countries and was followed by random selection of those health facilities in the study countries that had each recorded more than 1000 births in the previous year. All women who

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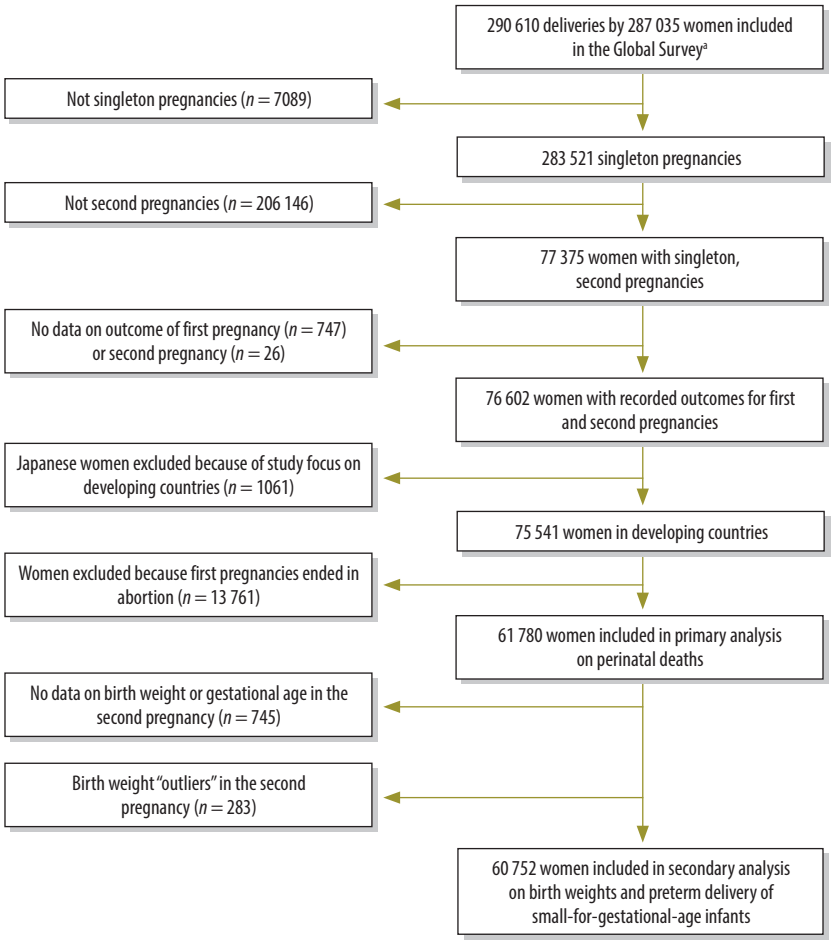
Fig. 1. **Flowchart showing the selection of study participants**



[a] Global Survey on Maternal and Perinatal Health.

had delivered at each of the 373 selected facilities during a specified period of 2 to 3 months were included in the survey and the corresponding mother–infant pairs were followed until the women were discharged or for a maximum of 7 days postpartum. In the time between delivery and discharge, trained data collectors transferred data on each mother–infant pair from the facility's routine medical records onto a standardized abstraction form. We tried to fill any gaps in the subjects' medical records via discussion with attending staff before the mothers were discharged.

For the Global Survey, data were collected on 290 610 births and 287 035 pregnancies. Study facilities were scattered across 24 countries in Africa (Algeria, Angola, Congo, Kenya, Niger, Nigeria and Uganda), Asia (Cambodia, China, India, Japan, Nepal, Philippines, Sri Lanka, Thailand and Viet Nam) and Latin America (Argentina, Brazil, Cuba, Ecuador, Mexico, Nicaragua, Paraguay and Peru). For the present analysis, all but one of the study countries (Japan) was categorized as "developing" and only complete data on singleton second pregnancies in the developing countries were included (Fig. 1).

Outcomes of the first pregnancy

For the first pregnancies, the main outcomes investigated were stillbirth (i.e. fetal death during or after week 22 of gestation), neonatal death (i.e. death of a liveborn infant at an age of < 28 days) and neonatal survival (i.e. infant living ≥ 28 days postpartum). The secondary outcome investigated – only for infants who lived for at least 28 days postpartum – was birth weight, which was categorized as very low, low and normal when < 1500, 1500–2499 and ≥ 2500 g, respectively.

Outcomes of the second pregnancy

For the second pregnancies, the main outcomes investigated were stillbirth, early neonatal death (i.e. death of a liveborn infant during the first 7 days of life) and admission of the infant to a neonatal ICU (or a similarly high level of care). The secondary outcomes investigated were birth-weight category (very low, low or normal) and the preterm delivery of an infant that was small for gestational age. There were 745 individuals with missing birth weights or gestational ages and 283 "outliers" who had birth weights that fell below percentile 0.001 or above percentile 99.999. This left 60 752 infants with valid gestational ages and birth weights for inclusion in our analyses (Fig. 1).

Small size for gestational age was defined as a birth weight below the 10th percentile of the continent-specific reference values for the same week of gestation. The reference values were determined using the singleton birth weights recorded in the Global Survey and a percentile calculator.[13] For week 40, the mean (and standard deviation, SD) singleton birth weights recorded in Africa (n = 24 221), Asia (n = 28 936) and Latin America (n = 26 122) were 3252.4 (480.0), 3099.1 (455.8) and 3346.2 (435.2) g, respectively.

Definitions of major covariates

All the major covariates that we assessed were variables examined for the second pregnancy. They included maternal sociodemographic factors, medical conditions and obstetric complications (see next section). Gestational age, in completed weeks, was based on the best obstetric estimate. Hypertensive disorders were categorized as chronic or as gestational hypertension, pre-eclampsia or eclampsia.

Statistical analysis

Statistical significance was investigated using mixed-model analysis-of-variance F-tests for the continuous variables and χ^2 tests for the categorical data (Table 1). We then used multinomial regressions to evaluate odds ratios (ORs) for very low and low birth weights (compared with normal birth weights; Table 2) and for stillbirth and early neonatal death (compared with neonatal survival; Table 3) in the second pregnancy, according to the outcome of the first pregnancy. Logistic regressions were used to evaluate the associations between previous pregnancy outcomes and the preterm delivery of an infant who was small for gestational age or admission of the infant to a neonatal ICU (Table 4).

Table 1. **Characteristics at second delivery of 61 780 women from 23 developing countries, 2004–2008**

Characteristic at second delivery	Women (%) whose first pregnancy was followed by:			*P*
	Stillbirth[a] (*n* = 1261)	Neonatal death[a] (*n* = 1052)	Neonatal survival[a] (*n* = 59 467)	
Mean age at delivery, years (SD)	25.1(5.1)	24.5(4.8)	26.2(5.0)	< 0.001
Mean infant birth weight, g (SD)	3001 (568)	2953 (605)	3115 (524)	< 0.001
Age (years)				< 0.001
< 18	2.1	2.7	1.5	
18–34	92.0	92.6	91.8	
≥ 35	5.9	4.8	6.7	
Marital status				< 0.01
Married	87.1	91.7	89.5	
Single	12.9	8.3	10.5	
Education (years)				< 0.001
≥ 7	66.8	65.5	72.8	
< 7	33.2	34.5	27.2	
Urinary infection	4.3	5.4	6.3	< 0.01
Any antenatal antibiotic treatment	8.6	8.3	9.0	0.64
Diabetes	0.7	1.0	0.6	0.25
Hypertensive disorder				< 0.001
None	91.6	92.9	95.0	
Chronic or gestational hypertension	4.1	3.5	2.7	
Pre-eclampsia	3.6	3.1	2.0	
Eclampsia	0.8	0.5	0.2	
Gestational age (weeks)				< 0.001
< 34	4.2	5.3	1.8	
34–36	9.7	9.3	7.0	
≥ 37	86.0	85.3	91.1	
Onset of labour				< 0.05
Spontaneous	77.3	82.6	80.4	
Induced	9.4	6.4	8.3	
No labour	13.3	11.0	11.3	
Pre-labour rupture of membranes	8.8	7.9	8.3	0.75
Fetal presentation at delivery				< 0.001
Cephalic	93.5	94.1	96.1	
Breech and other	6.5	5.9	3.9	
Mode of delivery				< 0.001
Vaginal	67.9	68.3	74.4	
Caesarean section	32.1	31.7	25.6	
Level of health facility				< 0.01
Primary or secondary	41.8	38.6	43.7	
Tertiary	53.1	55.2	50.0	
Other referral level	5.1	6.2	6.3	
Continent of residence				< 0.001
Africa	35.4	35.8	25.0	
Latin America	19.3	20.2	34.4	
Asia	45.2	43.9	40.6	
Outcome				
Small size for gestational age	10.0	14.0	9.3	< 0.001
Neonate admitted to ICU	13.7	13.5	7.8	< 0.001
Stillbirth	4.6	3.3	1.4	< 0.001
Early neonatal death	1.1	2.4	0.6	< 0.001

ICU, intensive-care unit; SD, standard deviation.

[a] All values in column are percentages except for maternal age at delivery and infant birth weight, which are expressed as means and SDs.

Table 2. **Associations between adverse outcomes in the first pregnancy (FP) and birth weight in the second pregnancy (SP), 23 developing countries, 2004–2008[a]**

Birth weight in SP and outcome of FP	No. (%) of infants with low birth weight in SP	OR (95% CI) from:		
		Unadjusted model	Model 1[b]	Model 2[c]
< 1500 g				
Infant alive at 28 days	468 (0.8)	1.00 (–)	1.00 (–)	1.00 (–)
Stillbirth	25 (2.0)	2.66 (1.78–3.98)	2.74 (1.85–4.07)	2.52 (1.68–3.76)
Neonatal death	24 (2.3)	3.17 (2.03–4.96)	2.99 (1.91–4.69)	2.78 (1.69–4.56)
1500–2499 g				
Infant alive at 28 days	4488 (7.7)	1.00 (–)	1.00 (–)	1.00 (–)
Stillbirth	132 (10.7)	1.46 (1.18–1.81)	1.35 (1.09–1.68)	1.22 (0.99–1.52)
Neonatal death	139 (13.5)	1.91 (1.57–2.34)	1.67 (1.37–2.04)	1.60(1.31–1.96)

CI, confidence interval; OR, odds ratio.

[a] No data on birth weights were available for 1028 second pregnancies. The data for the remaining 60 752 births in second pregnancies (517, 4759 and 55 476 with birth weights of < 1500, 1500–2499 and ≥ 2500 g, respectively) were included in the analysis. The corresponding first pregnancies had ended in stillbirth (n = 1232), neonatal death (n = 1029) or an infant who lived for at least 28 days postpartum (n = 58 491). The reference group comprised second pregnancies with birth weights of ≥ 2500 g.

[b] Adjusted for maternal age (< 18, 18–34 or ≥ 35 years), marital status, education (< 7 or ≥ 7 years or unknown), country of residence (22 indicator variables were generated for the 23 countries) and level of health facility (primary or secondary, tertiary or other referral level).

[c] Adjusted as for Model 1, with additional adjustments for diabetes, hypertensive disorders, mode of delivery, type of onset of labour, pre-labour rupture of membranes, fetal presentation at delivery, urinary infection, and any antenatal antibiotic treatment.

Table 3. **Associations between adverse outcomes in the first pregnancy and stillbirth or neonatal death in the second pregnancy (SP), 23 developing countries, 2004–2008[a]**

Pregnancy and outcome		No. (%) of women with outcome in SP	OR (95% CI) from:			
Second	First		Unadjusted model	Model 1[b]	Model 2[c]	Model 3[d]
Stillbirth	Infant alive at 28 days	817 (1.4)	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
	Stillbirth	58 (4.6)	3.48 (2.52–4.79)	2.79 (1.97–3.94)	2.35 (1.65–3.37)	1.91 (1.25–2.92)
	Neonatal death	35 (3.3)	2.52 (1.79–3.54)	1.81 (1.31–2.51)	1.73 (1.23–2.42)	1.08 (0.73–1.58)
Early neonatal death	Infant alive at 28 days	360 (0.6)	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
	Stillbirth	13 (1.0)	1.77 (1.01–3.10)	1.61 (0.90–2.89)	1.32 (0.74–2.35)	1.10 (0.56–2.17)
	Neonatal death	25 (2.4)	4.08 (2.70–6.17)	3.21 (2.03–5.08)	2.82 (1.76–4.52)	2.19 (1.29–3.73)

CI, confidence interval; OR, odds ratio.

[a] The data for 61 780 second pregnancies (910 and 398 of which ended in stillbirth and early neonatal death, respectively) were included in the analysis. The corresponding first pregnancies had ended in stillbirth (n = 1261), neonatal death (n = 1052) or an infant who lived for at least 28 days postpartum (n = 59 467). The reference group comprised the 60 472 second pregnancies in which the infant survived for at least 7 days postpartum.

[b] Adjusted for maternal age (< 18, 18–34 or ≥ 35 years), marital status, education (< 7 or ≥ 7 years or unknown), country of residence (22 indicator variables were generated for the 23 countries) and level of health facility (primary or secondary, tertiary or other referral level).

[c] Adjusted as for Model 1, with additional adjustments for diabetes, hypertensive disorders, mode of delivery, type of onset of labour, pre-labour rupture of membranes, fetal presentation at delivery, urinary infection, and any antenatal antibiotic treatment.

[d] Adjusted as for Model 2, with additional adjustments for small size for gestational age and gestational age (< 34, 34–36 or ≥ 37 weeks) in the second pregnancies.

We included covariates that were of a priori interest (Model 1) or that are known risk factors for adverse pregnancy outcomes (Model 2) in all of the logistic and multinomial regression models. Covariates in Model 1 included sociodemographic factors that may influence the outcomes of second pregnancies, such as maternal age (categorized as < 18, 18–34 or ≥ 35 years), marital status, years of education (categorized as < 7 or ≥ 7 or unknown), country of residence (22 indicator variables were generated for 23 countries), and the level of the health facility in which the second pregnancy was managed (categorized as primary, secondary, tertiary or "other"). In Model 2 we used the same covariates plus several maternal medical conditions and obstetric factors (pre-existing diabetes, hypertensive disorders, mode of delivery, type of onset of labour, pre-labour rupture of membranes, fetal presentation at delivery, urinary infection and antenatal antibiotic treatment). Since small size for gestational age and preterm birth are major risk factors for fetal and/or neonatal death,[14, 15] we investigated a third model (Model 3) that included small size for gestational age and preterm status (categorized as a gestational age at birth of < 34, 34–36 or ≥ 37 weeks), as well as all of the covariates included in Model 2 (Table 3).

Among the women who had first pregnancies that ended in neonate survival, we also investigated if very low or low birth weight in the first pregnancy was associated with stillbirth, preterm birth of a small-for-gestational age infant and/or admission of the infant to a neonatal ICU in the second pregnancy,

Table 4. **Associations between an adverse outcome in the first pregnancy and the preterm delivery of a small-for-gestational-age (SGA) infant or admission of the neonate to an intensive care unit (ICU) in the second pregnancy (SP), 23 developing countries, 2004–2008[a]**

Pregnancy and outcome		No. (%) of women with outcome in SP	OR (95% CI)		
Second	First		Unadjusted model	Model 1[b]	Model 2[c]
Preterm, SGA infant	Infant alive at 28 days	630 (1.1)	1.00 (–)	1.00 (–)	1.00 (–)
	Stillbirth	23 (1.9)	1.75 (1.19–2.58)	1.72 (1.17–2.53)	1.38 (0.88–2.15)
	Neonatal death	18 (1.8)	1.64 (0.94–2.83)	1.46 (0.86–2.47)	1.26 (0.72–2.23)
Admission of neonate to ICU	Infant alive at 28 days	4549 (7.8)	1.00 (–)	1.00 (–)	1.00 (–)
	Stillbirth	165 (13.7)	1.89 (1.37–2.60)	1.92 (1.50–2.45)	1.64 (1.26–2.13)
	Neonatal death	137 (13.5)	1.85 (1.48–2.31)	1.92 (1.57–2.35)	1.68 (1.38–2.04)

CI, confidence interval; OR, odds ratio.

[a] The data for 60 752 second pregnancies (671 of which ended in a preterm, SGA infant) and for 60 840 second pregnancies (4851 of which ended in neonatal admission to an ICU) were included in the analysis of size for gestational age and of neonatal ICU admissions, respectively. The corresponding first pregnancies had ended in stillbirth ($n = 1232$ for analysis of size for gestational age; $n = 1203$ for the ICU admission analysis), neonatal death ($n = 1029$ for the analysis of size for gestational age; $n = 1016$ for the ICU admission analysis) or an infant who lived for at least 28 days postpartum ($n = 58\,491$ for the analysis of size for gestational age and 58 621 for the ICU admission analysis). The reference group for the analysis of size for gestational age comprised the 60 079 second pregnancies in which the infant was not preterm and small for gestational age, whereas that for the ICU admission analysis comprised the 55 989 second pregnancies in which the neonate did not require admission to an ICU.

[b] Adjusted for maternal age (< 18, 18–34 or ≥ 35 years), marital status, education (< 7 or ≥ 7 years or unknown), country of residence (22 indicator variables were generated for the 23 countries) and level of health facility (primary or secondary, tertiary or other referral level).

[c] Adjusted as for Model 1, with additional adjustments for diabetes, hypertensive disorders, mode of delivery, type of onset of labour, pre-labour rupture of membranes, fetal presentation at delivery, urinary infection, and any antenatal antibiotic treatment.

Table 5. **Association between birth weight in the first pregnancy (FP) and outcome of the second pregnancy (SP), 23 developing countries, 2004–2008[a]**

Outcome of SP and birth weight in FP	No. (%) of women with outcome in SP	OR (95% CI) from:		
		Unadjusted model	Model 1[b]	Model 2[c]
Preterm, SGA infant				
≥ 2500 g	371 (0.8)	1.00 (–)	1.00 (–)	1.00 (–)
1500– 2499 g	114 (2.5)	3.11 (2.42–4.01)	2.75 (2.12–3.57)	2.52 (1.91–3.31)
< 1500 g	9 (3.7)	4.67 (2.43–8.99)	4.70 (2.43–9.08)	3.81 (1.88–7.74)
Admission of neonate to ICU				
≥ 2500 g	3210 (7.1)	1·00 (–)	1.00 (–)	1.00 (–)
1500–2499 g	420 (9.3)	1.34 (1.17–1.54)	1.48 (1.32–1.66)	1.44 (1.28–1.63)
< 1500 g	38 (16.1)	2.50 (1.77–3.53)	2.49 (1.73–3.60)	2.29 (1.55–3.38)
Stillbirth				
≥ 2500 g	559 (1.2)	1.00 (–)	1.00 (–)	1.00 (–)
1500–2499 g	88 (1.9)	1.57 (1.21–2.05)	1.31 (1.05–1.65)	1.30 (1.04–1.61)
< 1500 g	10 (4.1)	3.42 (1.79–6.52)	3.83 (1.96–7.47)	3.50 (1.85–6.62)

CI, confidence interval; ICU, intensive care unit; OR, odds ratio; SGA, small-for-gestational-age.

[a] The analysis was restricted to the women who, as a result of their first pregnancies, had a child who survived for at least 28 days postpartum. The children from these first pregnancies had birth weights of ≥ 2500 g ($n = 45\,041$–$45\,635$, depending on the second pregnancy outcome being considered), 1500–2499 g ($n = 4512$–4602) or < 1500 g ($n = 236$–246). In each model, the risk of each adverse outcome of the second pregnancy increased as the birth weight of the infant resulting from the first pregnancy decreased ($P < 0.001$ for each trend).

[b] Adjusted for maternal age (< 18, 18–34 or ≥ 35 years), marital status, education (< 7 or ≥ 7 years or unknown), country of residence (22 indicator variables were generated for the 23 countries) and level of health facility (primary or secondary, tertiary or other referral level).

[c] Adjusted as for Model 1, with additional adjustments for diabetes, hypertensive disorders, mode of delivery, type of onset of labour, pre-labour rupture of membranes, fetal presentation at delivery, urinary infection and any antenatal antibiotic treatment.

with adjustment for the same covariates considered in Model 1 or 2 (Table 5). Small sample sizes precluded an investigation of the association between neonatal death in the second pregnancy and low birth weight in the same pregnancy.

Generalized estimating equations were applied to all logistic and multinomial regression models and independence correlation structures were used to adjust for the variable correlation within each health facility. All of the data analysis was performed using version 9.1 of the SAS software package (SAS Institute, Cary, United States of America). A P-value of < 0.05 was considered indicative of a statistically significant difference or association.

Results

The present study was based on the data for 61 780 women who had been included in WHO's Global Survey on Maternal

and Prenatal Health as they experienced their second pregnancies. The mean age of these women at their second deliveries was 26.1 years (SD: 5.0 years). They lived in Africa (25.4%), Asia (40.7%) or Latin America (33.8%). In their first pregnancies, there had been 1261 stillbirths and 1052 neonatal deaths (Table 1). In their second pregnancies, there had been 910 stillbirths and 398 early neonatal deaths.

The women could be split into three groups according to the outcomes of their first pregnancies (i.e. whether the first pregnancies had ended in stillbirth, neonatal death or neonatal survival). Although these three groups of women showed similar frequencies of antenatal antibiotic treatment, diabetes and prelabour rupture of membranes in their second pregnancies ($P > 0.05$ for each), they differed significantly in terms of most of the maternal demographic variables, maternal medical conditions and obstetric factors that had been recorded for the second pregnancies and also in terms of the outcomes of their second pregnancies ($P \leq 0.05$ for each; Table 1).

In Model 2 – after adjusting for possible confounders and in comparison with the women whose first pregnancies had ended in neonate survival (Table 2) – the women who had previously suffered a stillbirth were found to be significantly more likely to have had a second pregnancy ending in the delivery of an infant with very low birth weight (OR: 2.52; 95% confidence interval, CI: 1.68–3.76) – but not more likely to have delivered an infant with low birth weight (OR: 1.22; 95% CI: 0.99–1.52). In the same model, and again in comparison with the women whose first pregnancies had ended in neonate survival (Table 2), the women who had previously suffered a neonatal death were found to be more likely to have had second pregnancies ending with the delivery of an infant with low birth weight (OR: 1.60; 95% CI: 1.31–1.96) or very low birth weight (OR: 2.78; 95% CI: 1.69–4.56). Of the infants delivered at the end of the second pregnancies, those born to women who had previously suffered a stillbirth or neonatal death were at increased risk of admission to an intensive-care unit (OR: 1.64 and 1.68, respectively; $P < 0.001$ for each; Table 4).

In their second pregnancies, in comparison with the women whose first pregnancies had ended in neonate survival, the women who had previously suffered a stillbirth were more likely to have had a stillbirth (4.6% versus 1.4%) and, similarly, the women who had previously suffered a neonatal death were more likely to have had an infant that died as a young neonate (2.4% versus 0.6%) (Table 1 and Table 3). The results from Model 1 indicate that, after adjustment for demographic variables and the level of the health facility where the delivery occurred – and in comparison with the women whose first pregnancies had ended in neonate survival – the odds of stillbirth in the second pregnancy were 2.79-fold higher (95% CI: 1.97–3.94) for the women who had already suffered a stillbirth and 1.81-fold higher (95% CI: 1.31–2.51) for the women who had previously suffered a neonatal death (Table 3). In comparison with the women whose first pregnancies had ended in neonate survival, the odds of early neonatal death in the second pregnancy were 3.21-fold higher (95% CI: 2.03–5.08) for the women who had already suffered a neonatal death but were not significantly higher (OR: 1.61; 95% CI: 0.90–2.89) for the women who had previously suffered a stillbirth (Table 3). These associations were found to be slightly weaker after the additional adjustments made – for known risk factors for stillbirth or neonatal death – in Model 2 (Table 3). In Model 3, the additional adjustments for small size for gestational age and preterm status further reduced the odds of the second pregnancy of a woman who had previously suffered a stillbirth ending in a second stillbirth – from an OR of 2.35 (95% CI: 1.65–3.37) to one of 1.91 (95% CI: 1.25–2.92) – and the odds of a woman who had previously suffered a neonatal death giving birth to a second child who died as a young neonate – from an OR of 2.82 (95% CI: 1.76–4.52) to an OR of 2.19 (95% CI: 1.29–3.73). However, the addition of small size for gestational age and preterm status to Model 3 left no significant association between neonatal death after the first pregnancy and stillbirth in the second pregnancy (Table 3).

In Model 2, after adjustment for possible confounders, the women whose infants were alive 28 days after their first pregnancies were found to be at increased risk of the preterm birth of an infant who was small for gestational age, infant admission to an ICU and stillbirth in their second pregnancies if their first child had a low or very low birth weight, than if that child had a normal birth weight (Table 5).

The associations that we detected appeared to be largely unaffected by the women's continent of residence (Table 6 and Table 7).

Discussion

In this study, women with an adverse outcome (i.e. stillbirth, neonatal death, infant with low birth weight and/or infant with very low birth weight) in their first pregnancy were found to be at increased risk of an adverse outcome (i.e. stillbirth, neonatal death, neonate requiring admission to an ICU, preterm birth of an infant that was small for gestational age, an infant with low birth weight or very low birth weight) in their second pregnancies, indicating that some of the adverse outcomes have causes in common. Of note, after adjusting for small size for gestational age, preterm status and other covariates, women who had had a first pregnancy that ended in a stillbirth still appeared to be at increased risk of stillbirth at the end of their second pregnancy, while women who had seen their first children die as neonates were at increased risk of seeing a live birth followed by early neonatal death in their second pregnancies.

In earlier investigations, perinatal deaths have been associated with an increased risk of low-birth-weight infants in subsequent pregnancies.[16, 17] Low birth weights probably reflect suboptimal fetal environments and/or short pregnancies.[18] Very low birth weights are generally preterm infants.[10] Even among the women whose first children survived for at least 28 days postpartum, there was a strong link between very low birth weights in the first pregnancy and the risk of stillbirth in the second pregnancy. These findings indicate that the causes of at least some perinatal deaths are related to the causes of very low birth weights.

In this study, recurrence associations for stillbirth and neonatal death were seen even after adjustment for the known risk factors for perinatal death and potential confounders. Stillbirths in the first two pregnancies may therefore have common biological causes beyond any known risk factors for stillbirth that may develop during the second pregnancy. This may also be true for neonatal deaths.

Although there have been a few previous population-based studies on

Table 6. **Associations between adverse outcomes of the first pregnancy (FP) and stillbirth in the second pregnancy, by continent, 23 developing countries, 2004–2008[a]**

Outcome of FP by continent	No. (%) of women with outcome	OR (95% CI) from:			
		Unadjusted model	Model 1[b]	Model 2[c]	Model 3[d]
Africa					
Infant alive at 28 days ($n = 14\,771$)	324 (2.2)	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Stillbirth ($n = 442$)	32 (7.2)	3.48 (2.32–5.21)	3.34 (2.18–5.12)	2.65 (1.64–4.27)	2.06 (1.21–3.49)
Neonatal death ($n = 367$)	14 (3.8)	1.77 (1.10–2.83)	1.68 (1.05–2.69)	1.53 (0.87–2.68)	1.05 (0.55–2.02)
Asia					
Infant alive at 28 days ($n = 23\,989$)	342 (1.4)	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Stillbirth ($n = 564$)	19 (3.4)	2.41 (1.36–4.27)	2.01 (1.06–3.79)	1.59 (0.86–2.91)	1.47 (0.69–3.15)
Neonatal death ($n = 451$)	19 (4.2)	3.04 (1.89–4.88)	2.08 (1.37–3.17)	1.90 (1.23–2.94)	1.14 (0.71–1.82)
Latin America					
Infant alive at 28 days ($n = 20\,347$)	151 (0.7)	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Stillbirth ($n = 242$)	7 (2.9)	3.98 (1.65–9.61)	4.17 (1.72–10.15)	3.70 (1.61–8.51)	3.08 (1.32–7.20)
Neonatal death ($n = 209$)	2 (1.0)	1.29 (0.18–9.16)	1.24 (0.18–8.78)	1.14 (0.17–7.49)	0.34 (0.07–1.70)

CI, confidence interval; OR, odds ratio.

[a] The data for 61 382 second pregnancies (910 of which ended in stillbirth) were included in the analysis. The reference group comprised the 60 472 second pregnancies in which the infant survived for at least 7 days postpartum.

[b] Adjusted for maternal age, marital status, education (< 7 or ≥ 7 years or unknown), country of residence (22 indicator variables were generated for the 23 countries) and level of health facility (primary or secondary, tertiary or other referral level).

[c] Adjusted as for Model 1, with additional adjustments for hypertensive disorders, mode of delivery, type of onset of labour, pre-labour rupture of membranes, fetal presentation at delivery, urinary infection, and any antenatal antibiotic treatment.

[d] Adjusted as for Model 2, with additional adjustments for small size for gestational age and gestational age (< 34, 34–36 or ≥ 37 weeks) in the second pregnancies.

Table 7. **Associations between adverse outcomes of the first pregnancy and early neonatal death in the second pregnancy, split according to continent, 23 developing countries, 2004–2008[a]**

Outcome of FP by continent	No. (%) of women with outcome	OR (95% CI) from:			
		Unadjusted model	Model 1[b]	Model 2[c]	Model 3[d]
Africa					
Infant alive at 28 days ($n = 14\,554$)	107 (0.7)	1.00	1.00	1.00	1.00
Stillbirth ($n = 415$)	5 (1.2)	1.65 (0.58–4.65)	1.72 (0.57–5.19)	1.45 (0.50–4.25)	1.56 (0.54–4.49)
Neonatal death ($n = 363$)	10 (2.8)	3.82 (1.81–8.07)	3.06 (1.33–7.04)	2.70 (1.08–6.72)	2.07 (0.65–6.55)
Asia					
Infant alive at 28 days ($n = 23\,797$)	150 (0.6)	1.00	1.00	1.00	1.00
Stillbirth ($n = 551$)	6 (1.1)	1.74 (0.80–3.75)	1.47 (0.67–3.19)	1.14 (0.54–2.41)	0.87 (0.34–2.25)
Neonatal death ($n = 443$)	11 (2.5)	4.01 (2.23–7.23)	3.27 (1.74–6.14)	2.60 (1.37–4.95)	2.30 (1.26–4.21)
Latin America					
Infant alive at 28 days ($n = 20\,299$)	103 (0.5)	1.00	1.00	1.00	1.00
Stillbirth ($n = 237$)	2 (0.8)	1.67 (0.43–6.53)	1.73 (0.45–6.74)	1.67 (0.43–6.55)	1.40 (0.31–6.33)
Neonatal death ($n = 211$)	4 (1.9)	3.79 (1.35–10.62)	3.83 (1.38–10.63)	3.98 (1.42–11.18)	2.92 (1.07–7.98)

CI, confidence interval; FP, first pregnancy; OR, odds ratio.

[a] The data for 60 870 second pregnancies (398 of which ended in early neonatal death) were included in the analysis. The reference group comprised the 60 472 second pregnancies in which the infant survived for at least 7 days postpartum.

[b] Adjusted for maternal age, marital status, education (< 7 or ≥ 7 years or unknown), country of residence (22 indicator variables were generated for the 23 countries) and level of health facility (primary or secondary, tertiary or other referral level).

[c] Adjusted as for Model 1, with additional adjustments for hypertensive disorders, mode of delivery, type of onset of labour, pre-labour rupture of membranes, fetal presentation at delivery, urinary infection, and any antenatal antibiotic treatment.

[d] Adjusted as for Model 2, with additional adjustments for small size for gestational-age and gestational age (< 34, 34–36 or ≥ 37 weeks) in the second pregnancies.

stillbirth recurrence in the second pregnancy, the findings were inconsistent.[7,19] In a study in the Grampian region of Scotland, in the United Kingdom of Great Britain and Northern Ireland, no association was detected between stillbirth in one pregnancy and the risk of stillbirth in the subsequent pregnancy.[7] In an analysis of data collected across Scotland, however, women who had previously suffered a stillbirth were found to be almost twice as likely to have a pregnancy ending in stillbirth (OR: 1.94; 99% CI: 1.29–2.92) than women who had no history of stillbirths.[8] The present results indicate that – in developing countries at least – stillbirths in first pregnancies are often predictors of the same adverse outcome in second pregnancies. The strength of this association in our study population was similar to that reported

in a study of national data from Sweden[19] but weaker than that reported in a study based in the state of Missouri, in the USA (OR: 5.8; 95% CI: 3.7–9.0).[20]

Our findings appear to be biologically plausible. Stillbirths have diverse etiologies.[19,21–23] Although we adjusted in our analysis for many maternal and fetal factors, there were still a few factors that we did not take into account. For example, we did not consider the impact of genetic abnormalities and birth defects, which are known to recur through multiple pregnancies.[24] In addition, > 20% of stillbirths are currently "unexplained" by maternal, obstetric, placental or fetal factors.[25,26] Although there is no available evidence to support this possibility, a previous history of stillbirth may still be a useful predictor of even these "unexplained" stillbirths.

Since they are at increased risk of an adverse outcome in their second pregnancies, women who have suffered an adverse outcome in their first pregnancies should be immediately identified as "at-risk", offered educational materials/pamphlets – and/or be invited to attend educational courses – on the risks and prevention of adverse outcomes in pregnancy, and be encouraged to attend a hospital for any subsequent deliveries and, if appropriate and possible, be offered emergency obstetric care for subsequent pregnancies.[5,27] It is also important to raise awareness at the community level of the risks and needs of such women. Home visits for women and children and the participation of women's groups have been identified as useful, evidence-based, community strategies for reducing reproductive, maternal, neonatal and child mortality and for promoting reproductive health.[6]

In this study, controlling for maternal medical conditions and pregnancy complications weakened the association between stillbirth in the first pregnancy and the preterm delivery of an infant who was small for gestational age at the end of the second pregnancy (Table 4). Similarly, controlling for small size for gestational age and preterm status weakened the association between death of the neonate after the first pregnancy and stillbirth in the second pregnancy (Table 3). It therefore appears that maternal medical conditions, pregnancy complications, small size for gestational age and preterm (especially very preterm) delivery may play a substantial role in the occurrence of perinatal death.

The present study appears to be the first multinational investigation of the recurrence of adverse pregnancy outcomes in developing countries. Its strengths include the large sample size, the consideration of multiple, maternal, medical and obstetric factors, and its use of fairly detailed information on pregnancy outcomes and neonatal mortality. The data on second pregnancies that were used in the analysis were all collected over a period of just 2–3 months. This minimized the potentially confusing effects of any long-term trends that may have occurred in the variables that were recorded, such as decreases in stillbirth rates as the general levels of health care gradually improved.[28]

Our study also had several limitations. To be included in the study, a woman had to have delivered at a health facility that dealt with ≥ 1000 births per year. This inclusion criterion excluded data from very small hospitals and home births. Consequently, the findings may not be generalized to the countries and continents involved in this study, especially not to those countries where delivery in a health facility is the exception rather than the norm. We could not make any allowance for the effects of maternal smoking, the mother's body mass index before she became pregnant or the interval between the mother's first and second pregnancies, since no data on these variables were recorded in the Global Survey. However, smoking and pre-pregnancy body mass index are known to have an impact on two of the covariates that we did consider in some of our models: small size for gestational age and preterm status.[11,29,30] In the present study, size for gestational age status may have been recorded inaccurately for antepartum stillbirths because, for the infants concerned, gestational age at delivery may have been longer than gestational age at death. Such inaccuracy may have led to the misclassification of some stillborns as small for gestational age. Finally, no account was taken of the duration of each woman's hospitalization for her deliveries although, in countries where women who have been admitted for delivery are generally discharged a few days postpartum, many neonatal deaths may occur at home and never be listed in the woman's medical records. In China, for example, around 17% of the infants born in urban hospitals were found to have died at home during their first 28 days of life.[31] If, in the present study, mothers had been discharged before their infants had died aged < 7 days, the outcomes of their pregnancies would have been incorrectly recorded as neonate survival. However, the number of early neonatal deaths missed because of rapid discharge from Chinese hospitals should have been relatively small because about 63% of neonatal deaths in China occur within 2 days of birth.[31]

In conclusion, analyses of data collected as part of the WHO's Global Survey on Maternal and Prenatal Health indicate that an adverse outcome in the first pregnancy of a woman living in the developing world is often a predictor of an adverse outcome in that woman's second pregnancy. A woman whose first pregnancy had ended in a stillbirth or in the birth of an infant who died as a neonate was at increased risk of suffering exactly the same tragedy in her second pregnancy. The identification of such women before they become pregnant for a second time would allow them to be closely monitored for various fetal and maternal complications, with the aim of increasing the chances that the women would subsequently deliver healthy infants. ■

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ملخص

معاودة الإصابة بالحصائل السلبية في الفترة المحيطة بالولادة في البلدان النامية

الغرض تقييم خطورة معاودة الإصابة بالحصائل السلبية في الفترة المحيطة بالولادة في الحمل الثاني في البلدان النامية.

الطريقة تم استخدام البيانات الواردة من الدراسة الاستقصائية العالمية المعنية بالأمومة والصحة في الفترة المحيطة بالولادة في الفترة من 2004 إلى 2008 لتحديد حصائل الحمل الثاني المنفرد لعدد 61780 امرأة في 23 بلداً نامياً. وتم متابعة أزواج الأمهات وأطفالهن الرضع حتى الخروج من المستشفى أو لمدة 7 أيام بعد الوضع.

النتائج في نهاية حملهن الثاني، كانت السيدات اللاتي انتهى حملهن الأول بالإملاص (العدد = 1261) أو تبعه وفاة المواليد (العدد = 1052) أكثر احتمالاً لولادة طفل يزيد وزنه عند الميلاد عن 1500 جم عن السيدات اللاتي لم يتعرضن لأي من هذه الحصائل (نسبة الاحتمال: 2.52 و2.78، على التوالي) أو 1500 إلى 2499 جم (نسبة الاحتمال: 1.22 و1.60، على التوالي) أو رضيعاً يحتاج إلى الدخول إلى وحدة الرعاية المركزة (نسبة الاحتمال: 1.64 و1.68، على التوالي). وفي نهاية الحمل الثاني، تعرضت السيدات اللاتي انتهى حملهن الأول بإملاص إلى ازدياد مخاطر وقوع إملاص آخر (نسبة الاحتمال: 2.35) وتعرضت السيدات اللاتي توفي رضيعهن الأول في مرحلة الوليد الجديد إلى ازدياد مخاطر ولادة الرضيع الثاني متوفياً في غضون السبعة أيام الأولى من حياته (نسبة الاحتمال 2.82). وتبين أن هذه الاتجاهات لم تتأثر بشكل واسع بالقارة التي تعيش فيها السيدات.

الاستنتاج في العالم النامي، تتعرض السيدات اللاتي ينتهي حملهن الأول بالإملاص أو يتبعه وفاة المواليد الجديدة إلى ازدياد مخاطر وقوع الحصائل ذاتها في حملهن الثاني.

摘要

发展中国家不良围生期结局复发

目的 评估发展中国家第二次怀孕围生期不良结局复发的风险。

方法 使用孕产妇和围生期卫生2004－2008 年全球调查的数据确定在23 个发展中国家61780 名妇女单胎第二次怀孕的结局。对母婴对随访至出院或者进行7 天的产后随访。

结果 在第二次怀孕结束时，在第一次怀孕中有过死产的妇女（n＝1261）或者新生儿死亡（n＝1052）的妇女比没有经历此类结局的妇女的婴儿更有可能生产体重＜1500 g（优势比，OR：分别为2.52 和2.78）或者体重为1500－2499 g（OR：分别为1.22 和1.60）的婴儿，或生出的婴儿更可能需要进入特护病房（OR：分别为1.64 和1.68）。在其第二次妊娠晚期，在第一次怀孕时发生过死产的妇女再次发生死产的风险更高（OR：2.35），而第一个婴儿初生夭折的妇女，其第二个婴儿也更有可能在第一周内死亡（OR：2.82）。产妇具体在哪个大洲基本上不影响这些趋势。

结论 在发展中国家，妇女第一胎死产或者初生夭折，则在其第二次怀孕中经历同样结局的风险更大。

Résumé

Récurrence des issues périnatales indésirables dans les pays en développement

Objectif Évaluer le risque de récidive des issues périnatales indésirables lors des deuxièmes grossesses dans les pays en développement.

Méthodes Les données de l'Enquête mondiale sur la santé maternelle et périnatale menée sur la période 2004-2008 ont été utilisées pour déterminer les résultats des deuxièmes grossesses uniques auprès de 61 780 femmes dans 23 pays en développement. Les couples mère-enfant ont été suivis jusqu'à la fin de leur hospitalisation ou encore pendant 7 jours après l'accouchement.

Résultats À la fin de leur deuxième grossesse, les femmes dont la première grossesse s'était terminée par la naissance d'un enfant mort-né (n = 1 261) ou par la mort du nourrisson (n = 1 052) étaient plus susceptibles que les femmes ne se trouvant dans aucun de ces cas de figure de donner naissance à un enfant dont le poids de naissance serait inférieur à 1 500 g (rapport des cotes, RC: 2,52 et 2,78, respectivement) ou compris entre 1 500 et 2 499 g (RC: 1,22 et 1,60, respectivement), ou de donner naissance à un enfant nécessitant une admission dans une unité de soins intensifs (RC: 1,64 et 1,68, respectivement). À la fin de leur deuxième grossesse, les femmes dont la première grossesse s'était terminée par une mortinaissance couraient un risque accru de redonner naissance à un enfant mort-né (RC: 2,35), et celles dont la première grossesse s'était terminée par la mort du nourrisson couraient un risque accru de voir leur deuxième enfant mourir dans les 7 jours suivant l'accouchement (RC: 2,82). Ces tendances ne semblent vraisemblablement pas affectées par le continent sur lequel ces femmes vivent.

Conclusion Dans les pays en développement, une femme dont la première grossesse se termine par la naissance d'un enfant mort-né ou par la mort du nourrisson présente un risque accru de subir la même issue périnatale lors de sa deuxième grossesse.

Резюме

Повторение неблагоприятных перинатальных исходов в развивающихся странах

Цель Оценить риск повторения неблагоприятных перинатальных исходов в ходе второй беременности в развивающихся странах.

Методы Данные, полученные из проведенного в 2004-2008 годах Глобального обследования материнского и перинатального здоровья, были использованы для определения исходов одноплодной второй беременности 61 780 женщин в 23 развивающихся странах. Наблюдение за парами «мать-ребенок» велось до выписки или истечения 7 дней после родов

Результаты В конце своей второй беременности женщины, у которых первая беременность закончилась мертворождением

(n = 1261) или последующей смертью новорожденного (n = 1052), были более склонны, чем женщины, которые не сталкивались с таким результатом, к рождению ребенка с весом при рождении менее 1500 г (относительный риск (ОР) составил 2,52 и 2,78, соответственно) или 1500-2499 г (ОР — 1,22 и 1,60, соответственно), или же ребенку потребовалась реанимация (ОР — 1,64 и 1,68, соответственно). В конце своей второй беременности те женщины, чья первая беременность закончилась мертворождением, были подвержены повышенному риску повторного мертворождения (ОР = 2,35), а те женщины, чей первый новорожденный ребенок умер, были подвержены повышенному риску смерти второго ребенка в течение первых 7 дней жизни (ОР = 2,82). Эти тенденции преимущественно не зависят от континента проживания женщин.

Вывод В развивающихся странах женщина, у которой первая беременность заканчивается мертворождением или сопровождается смертью новорожденного, подвержена риску столкнуться с тем же результатам в ходе второй беременности.

Resumen

La recurrencia de los resultados perinatales adversos en países en desarrollo

Objetivo Evaluar el riesgo de recurrencia de los resultados perinatales adversos de los segundos embarazos en países en desarrollo.

Métodos Se emplearon datos de la Encuesta Global en Salud Materna y Perinatal realizada entre 2004 y 2008 para determinar los resultados del segundo embarazo de feto único de 61 780 mujeres en 23 países en desarrollo. Se hizo un seguimiento de cada par madre-niño hasta el alta de la madre o durante los 7 días posteriores al parto.

Resultados Al término de sus segundos embarazos, aquellas mujeres cuyo primer embarazo había terminado en muerte prenatal (n = 1261) o al cual le había sucedido una muerte neonatal (n = 1052) tenían más probabilidad de dar a luz a un niño con un peso inferior a 1500 g (cociente de probabilidades, CP: 2,52 y 2,78, respectivamente), entre 1500 y 2499 g (CP: 1,22 y 1,60, respectivamente), o a un niño que necesitara ser ingresado en la unidad de cuidados intensivos (CP: 1,64 y 1,68, respectivamente). Al final de sus segundos embarazos, las mujeres cuyo primer embarazo había terminado en muerte prenatal presentaron un riesgo mayor de sufrir otra muerte prenatal (CP: 2,35), y aquellas cuyo primer bebé había fallecido como neonato presentaron un riesgo mayor de que el segundo niño falleciera en los primeros siete días de vida (CP: 2,82). Se descubrió que el continente en el que vivían las mujeres no afectó en gran medida a estas tendencias.

Conclusión En el mundo en desarrollo, una mujer cuyo primer embarazo finaliza en muerte neonatal o al cual le sucede la muerte del neonato presenta un riesgo superior de volver a experimentar los mismos resultados en el segundo embarazo.

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