Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study

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Summary

Background We report the main findings of the WHO Multicountry Survey on Maternal and Newborn Health (WHOMCS), which aimed to assess the burden of complications related to pregnancy, the coverage of key maternal health interventions, and use of the maternal severity index (MSI) in a global network of health facilities.

Methods In our cross-sectional study, we included women attending health facilities in Africa, Asia, Latin America, and the Middle East that dealt with at least 1000 childbirths per year and had the capacity to provide caesarean section. We obtained data from analysis of hospital records for all women giving birth and all women who had a severe maternal outcome (SMO; ie, maternal death or maternal near miss). We regarded coverage of key maternal health interventions as the proportion of the target population who received an indicated intervention (eg, the proportion of women with eclampsia who received magnesium sulphate). We used areas under the receiver operator characteristic curves (AUROC) with 95% CI to externally validate a previously reported MSI as an indicator of severity. We assessed the overall performance of care (ie, the ability to produce a positive effect on health outcomes) through standardised mortality ratios.

Results From May 1, 2010, to Dec 31, 2011, we included 314 623 women attending 357 health facilities in 29 countries (2538 had a maternal near miss and 486 maternal deaths occurred). The mean period of data collection in each health facility was 89 days (SD 21). 23 015 (7·3%) women had potentially life-threatening disorders and 3024 (1·0%) developed an SMO. 808 (26·7%) women with an SMO had post-partum haemorrhage and 784 (25·9%) had pre-eclampsia or eclampsia. Cardiovascular, respiratory, and coagulation dysfunctions were the most frequent organ dysfunctions in women who had an SMO. Reported mortality in countries with a high or very high maternal mortality ratio was two-to-three-times higher than that expected for the assessed severity despite a high coverage of essential interventions. The MSI had good accuracy for maternal death prediction in women with markers of organ dysfunction (AUROC 0·826 [95% CI 0·802–0·851]).

Interpretation High coverage of essential interventions did not imply reduced maternal mortality in the health-care facilities we studied. If substantial reductions in maternal mortality are to be achieved, universal coverage of life-saving interventions need to be matched with comprehensive emergency care and overall improvements in the quality of maternal health care. The MSI could be used to assess the performance of health facilities providing care to women with complications related to pregnancy.

Funding UNDP–UNFPA–UNICEF–WHO–World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP); WHO; USAID; Ministry of Health, Labour and Welfare of Japan; Gynuity Health Projects.

Introduction

In recent years, two important changes in maternal health have taken place worldwide: first, a substantial reduction in global maternal mortality and second an increase in the proportion of childbirths occurring in health facilities.[1] Although substantial progress has been made, not enough has been done to meet the fifth Millennium Development Goal. An estimated 287 000 women died in 2010 of causes related to pregnancy and childbirth and a substantial proportion of childbirths still occur in communities without skilled birth assistance.[1] In this context, improving quality of care has become increasingly important to accelerate reduction in maternal mortality, to reduce maternal deaths in health facilities, and stimulate demand for institutional births.[2–5] In many settings, women prefer to deliver in the community because of concerns about perceived quality of care in health facilities.[5]

Good quality of care is a multidimensional notion that includes, among other factors, appropriate use of effective clinical and non-clinical interventions and strengthened health infrastructure and attitude of health providers, resulting in satisfaction of patients and providers and improved health outcomes.[6–7] As part of strategies to improve maternal health care, great emphasis has been placed on maximising coverage of life-saving maternal health interventions (eg, uterotonics for prevention and treatment of post-partum haemorrhage or magnesium sulphate for prevention and treatment of eclampsia).[8] Although coverage can be objectively monitored and assessed, other dimensions of quality are hard to measure.

Despite the global nature of the issue, maternal deaths are relatively rare events in individual facilities, complicating the assessment of effects of care on mortality. To overcome this epidemiological challenge, the notion of a near-miss event was introduced in maternal health, which is potentially able to complement the information obtained with reviews of maternal deaths.[9] In 2004, the WHO published a systematic review[10] about the prevalence of severe maternal morbidity and maternal near miss. In that review, the absence of standard definitions for both severe maternal morbidities and near-miss cases was a major constraint for obtaining an overall prevalence of these conditions. This difficulty led WHO to develop a standard definition of maternal near miss, based on markers of organ dysfunction (ie, survivors of organ dysfunction during pregnancy, childbirth, or after birth are classified as maternal near-miss cases).[11] The WHO criteria for maternal near miss were developed through an international consultative process, which also included systematic reviews,[10,12] pilot studies,[13,14] and a multicentre validation study.[15] Through coupling of maternal deaths and near-miss cases (both regarded as severe maternal outcomes [SMO]) and assessing their similarities and differences, a more robust analysis of the quality of maternal health care and its determinants can be made.[11,15] This collaborative effort allowed the development of the maternal severity index (MSI) model, which estimates the death probability of women with complications related to pregnancy.[15] Comparison of observed mortality to the model-estimated mortality allows investigators to make an overall assessment of performance.[15–17]

The main goal of this study, the WHO Multicountry Survey on Maternal and Newborn Health (WHOMCS), was to characterise the severe maternal, perinatal, and neonatal morbidity that occurs in a worldwide network of health facilities. Our analysis specifically aimed to describe maternal characteristics and perinatal outcomes, assesses the prevalence and severity of complications related to pregnancy, determines the coverage of key maternal health interventions, tests and externally validates the MSI model, and assesses the overall performance of care in participating facilities.

Methods

Study design and participants

The study protocol and other methodological details of the WHOMCS have been published previously.[18] Briefly, the study was a cross-sectional analysis implemented in health facilities in 29 countries from Africa, Asia, Latin America, and the Middle East. Figure 1 shows countries included in this study, stratified by level of maternal mortality ratio (MMR).[1] Most participating health facilities had also taken part in the previous WHO Global Survey on Maternal and Perinatal Health (2004–08).[19] Countries, provinces (or other equivalent political divisions within countries), and health facilities were randomly selected through a stratified, multistage cluster sampling strategy. Health facilities were only eligible if they dealt with at least 1000 deliveries per year and had the capacity to provide caesarean section. All women who gave birth at participating facilities (and their newborn babies) and all women with SMO made up the study population. In this analysis, we excluded second or higher order infants, but first-born babies and mothers were included. We defined women with SMO as having had a maternal death or maternal near miss up to 7 days after giving birth or having an abortion, irrespective of gestational age or delivery status. We defined maternal near-miss cases as women who survived a life-threatening condition (as identified by any marker of organ dysfunction and listed in the appendix). Women admitted to participating facilities after 7 days of termination of pregnancy (delivery or abortion) were not eligible for inclusion.

The HRP specialist panel (WHO scientific staff and external, independent researchers) on epidemiological research reviewed and approved the study protocol for technical content. This study was approved by the WHO ethical review committee and the relevant ethical clearance mechanisms in all countries. Written consent from individual participants was not required. Hospitals obtained the relevant clearances to participate.

Procedures

During the period of data collection, data collectors (trained by study country coordinators) undertook daily visits to obstetrical or post-partum wards, gynaecological or abortion care units, delivery rooms, emergency or intensive-care units to identify eligible women. We used paper forms to obtain data related to demographic and reproductive characteristics, pregnancy and childbirth status, pregnancy complications and their management, and morbidity and mortality of mothers and newborn babies in hospitals. We obtained data for all eligible study participants from hospital records at hospital discharge, transfer, or death up to 7 days post partum for both mother and baby. Data collectors consulted facility medical staff about missing or unclear information

Lancet 2013; 381: 1747–55

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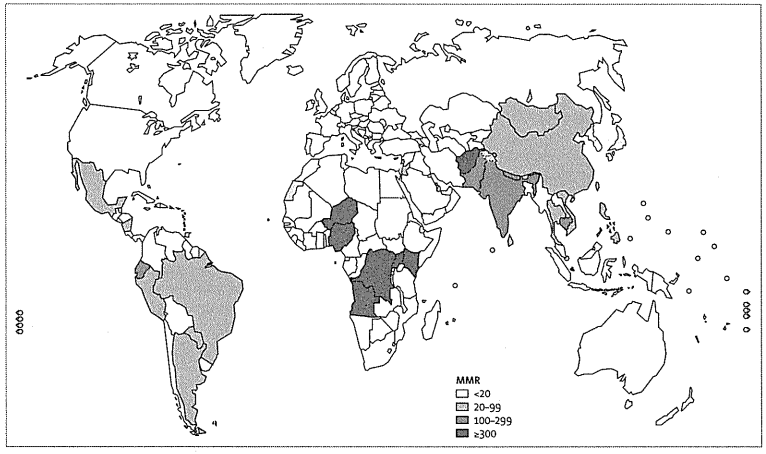

Figure 1: **Countries included in the WHO Multicountry Survey on Maternal and Newborn Health**
Countries are stratified by MMR (deaths per 100 000 livebirths). MMR=maternal mortality ratio.

during data collection. A manual of operations for data collectors was developed and used to reduce the need for judgment and interpretation. The data collection techniques were pretested on a convenient sample of records and clinical settings before the study. Training workshops at country and facility level were done and tailored according to specific needs. In each country, a short pilot phase was implemented to test the overall data management process. We undertook intra-form validity cross-checks in addition to random cross-checks comparing hospital records against recorded data. Because most of the facilities in WHOMCS had participated in the WHO Global Survey,[19] we emphasised training in the facilities that were new to the network.

Data were entered into a web-based data management system developed by the Centro Rosarino de Estudios Perinatales (CREP, Rosario, Argentina). Data entry was done at the health facility or at a central level, dependent on logistics and available infrastructure. Data managers in Argentina (LC, CCu, and DG) and Thailand (ML and NI) monitored the study data flow and data quality by use of validation procedures and progress reports for all countries. Data inconsistencies were identified and corrected by contacting centres as they occurred. These procedures have been used in previous multicentre studies, including the WHO Global Survey.[19]

Statistical analysis

Because the primary objectives of the WHOMCS were wide-ranging and related to maternal mortality and severe morbidity, which are relatively rare events in individual health facilities, a very large sample size was necessary to capture a statistically meaningful number of maternal deaths and near-miss cases. Based on previous maternal near-miss studies and the WHO Global Survey,

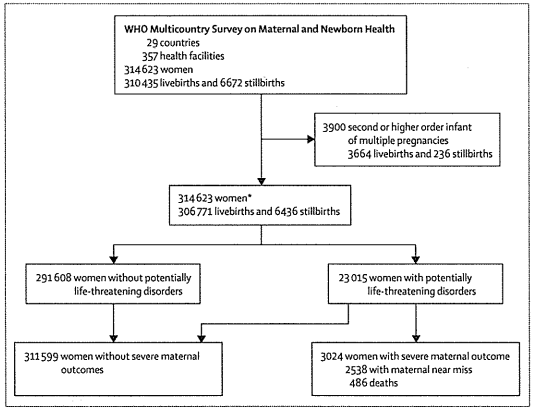

Figure 2: **Study profile**
*Sum of livebirths and stillbirths does not equal the number of women because some women had abortions or did not have a delivery.

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See Online for appendix

	All women	Women without an SMO	Women with an SMO	p value
Women	314 623 (100·0%)	311 599 (99·0%)	3024 (1·0%)	
Age				<0·0001
Data available	313 689	310 672	3017	
<20 years	32 328 (10·3%)	32 048 (10·3%)	280 (9·3%)	
20–35 years	254 307 (81·1%)	252 054 (81·1%)	2253 (74·7%)	
>35 years	27 054 (8·6%)	26 570 (8·6%)	484 (16·0%)	
Marital status				0·0337
Data available	310 934	307 956	2978	
Without partner	31 693 (10·2%)	31 458 (10·2%)	235 (7·9%)	
With partner	279 241 (89·8%)	276 498 (89·8%)	2743 (92·1%)	
Schooling				<0·0001
Data available	288 775	286 075	2700	
<5 years	58 630 (20·3%)	57 500 (20·1%)	1130 (41·9%)	
5–8 years	65 718 (22·8%)	65 137 (22·8%)	581 (21·5%)	
9–11 years	73 611 (25·5%)	73 101 (25·6%)	510 (18·9%)	
>11 years	90 816 (31·4%)	90 337 (31·6%)	479 (17·7%)	
Number of previous births				<0·0001
Data available	313 969	310 955	3014	
0	132 672 (42·3%)	131 692 (42·4%)	980 (32·5%)	
1–2	130 245 (41·5%)	129 220 (41·6%)	1025 (34·0%)	
>2	51 052 (16·3%)	50 043 (16·1%)	1009 (33·5%)	
Number of previous caesarean sections				<0·0001
Data available	310 355	307 364	2991	
0	272 302 (87·7%)	269 806 (87·8%)	2496 (83·5%)	
1	29 307 (9·4%)	28 987 (9·4%)	320 (10·7%)	
>1	8746 (2·8%)	8571 (2·8%)	175 (5·9%)	
Onset of labour				<0·0001
Data available	312 581	310 845	1736	
Spontaneous	241 724 (77·3%)	240 794 (77·5%)	930 (53·6%)	
Induced	32 784 (10·5%)	32 556 (10·5%)	228 (13·1%)	
Caesarean section with no labour	38 073 (12·2%)	37 495 (12·1%)	578 (33·3%)	
Mode of delivery				<0·0001
Data available	312 660	310 955	1705	
Vaginal	223 145 (71·4%)	222 505 (71·6%)	640 (37·5%)	
Caesarean section	89 515 (28·6%)	88 450 (28·4%)	1065 (62·5%)	

SMO=severe maternal outcome (ie, maternal near miss or maternal death).

Table 1: **Demographic and labour characteristics of women, according to maternal outcome**

the target sample size was estimated at 275 000 women to capture at least 2000 women with an SMO.[13,19,20] To reduce variation in cluster size, we collected data for a period of 2 months in facilities that had at least 6000 deliveries every year and for 3 months in facilities with fewer than 6000 deliveries every year. In countries where a 3 month collection period was anticipated to include fewer than 3000 deliveries overall, we extended the period to 4 months in all health facilities.

We used frequencies to describe maternal characteristics, modes of onset of labour and delivery, and perinatal outcome, with stratification by the maternal outcome. We used frequencies to describe the proportion of women affected by specific types of morbidities and assessed the distribution of selected pregnancy-related complications (ie potentially life-threatening conditions) in women without SMO, maternal near-miss cases, and maternal deaths. We stratified frequencies by MMR group to further explore the reported associations.

We calculated the frequency of women with potentially life-threatening conditions per 1000 livebirths, the maternal near-miss ratio (ie, number of maternal near-miss cases per 1000 livebirths), the severe outcome ratio (SMOR; number of SMOs per 1000 livebirths) and the intra-hospital MMR (ie, number of maternal deaths that took place in-hospital per 100 000 liverbirths, limited to the first 7 post-partum days). To complement this analysis, we assessed the severity of cases with organ dysfunction with the maternal severity score (MSS) and MSI. The MSS is the total number of markers of organ dysfunction; highest scores suggest highest severity and mortality.[15] The MSI is the probability of maternal death for each woman as estimated by the MSI model.[15]

We determined coverage of key maternal health interventions as the proportion of the target population who received the indicated intervention (ie, the proportion of women giving birth who received a prophylactic uterotonic, the proportion of women with post-partum haemorrhage who received a therapeutic uterotonic, the proportion of women with eclampsia who received magnesium sulphate, the proportion of women giving birth by caesarean section who received a prophylactic antibiotic, and the proportion of women with sepsis who received a parenteral antibiotic).

We defined a missed opportunity of care as an event in which a woman did not receive an indicated essential intervention (eg, a woman giving birth who did not receive a prophylactic uterotonic or a woman with eclampsia who did not receive magnesium sulphate). We determined the proportion of women with SMO with at least one missed opportunity of care and assessed the risk of mortality associated with these missed opportunities.

The MSI model was developed in a large, multicentre study[15] in Brazil to assess ability of a health service for management of women with life-threatening complications related to pregnancy. It was developed with binary logistic regression and internally validated through random split-sample methods. In the present study, we applied the previously reported MSI model in this independent multicountry population database to assess health service performance in a wide range of settings. Because the MSI model was developed in a country with moderate maternal mortality, we used the standardised mortality ratio (SMR) of countries with moderate MMR (ie, 20–100 deaths per 100 000 livebirths) to assess the calibration of the MSI estimates. The SMR is the ratio between observed maternal mortality risk and predicted maternal mortality risk—ie, SMR is equal to the number of observed maternal deaths per population size divided by the predicted number of maternal deaths per population size (which can be simplified to the number of observed

maternal deaths divided by the number of predicted maternal deaths); the predicted number of maternal deaths is equal to MSI×population size. In a population receiving a level of care equivalent to the level of care received by the population in which the MSI model was developed, the MSI model is expected to predict a similar number of maternal deaths by comparison with the reported number of maternal deaths (ie, SMR ~1·0).[15–17] We used the area under the receiver operator characteristics curves (95% CI) to externally validate the MSI as indicators of severity in this multicountry population and show its capacity to predict maternal deaths in women with organ dysfunction related to pregnancy.[16]

We assessed overall care performance (ie, ability to produce a positive effect in health outcomes) with the SMR. An SMR of about 1·0 suggests an intermediate performance of care (ie, an observed mortality akin to the expected for the level of severity, in countries with moderate MMR). Low SMRs suggest good performance of care (ie, an observed mortality lower than expected for the level of severity) and high SMRs suggest poor performance of care (ie, an observed mortality higher than expected for the level of assessed severity).[17]

Because health facilities were the primary sampling unit of this study, we assumed that individual-level analyses might have been affected by cluster effects.[21] Therefore, we adjusted all estimates of association for cluster effect (health facilities as the primary sampling unit with stratification by country). We corrected the Pearson χ^2 statistic for the survey design with the Rao-Scott correction, following the standard procedure in Stata statistical software.[22] Other *F* tests were corrected by dividing the *F* statistic by the design effect (ie, designed effect=1+(n−1)×ICC, where n is the average cluster size and ICC is the intracluster correlation coefficient).[23] We used logistic regression, with the "svy logistic" procedure in Stata statistical software, to generate odds ratio estimates accounting for multistage cluster sampling. Because the SMR is a risk ratio involving low or very low rates of events at the level of MMR country groups, we calculated estimates of SMR standard errors with Mantel-Haenszel methods at that level; we generated overall SMR estimates with random-effects models.

Statistical analyses were done with PASW statistics 18, release version 18.0.0 (SPSS, Chicago, IL, USA), Stata statistical software, release 11 (StataCorp, College Station, TX, USA), and RevMan version 5·2 (Cochrane Collaboration, Copenhagen, Denmark).

Role of the funding source

The sponsors had no role in data collection, analysis, or interpretation of the data, the writing of the report, or the decision to submit for publication. All authors had access to the analysis plan, the outputs of that analysis, and could see the full data if they wished to do so. All authors participated in the final discussion and approved the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	All women		Women without an SMO		Women with an SMO		p value
	N	Events per 1000 livebirths	n	Events per 1000 livebirths	n	Events per 1000 livebirths	
Livebirths	306 771	..	305 369	..	1402	..	..
Early neonatal deaths	2712	8·8	2623	8·6	89	63·5	<0·0001
Fetal deaths	6436	21·0	5918	19·4	518	369·5	<0·0001
Perinatal deaths*	7935	25·9	7414	24·3	521	371·6	<0·0001
Preterm births	20 941	68·3	20 542	67·3	399	284·6	<0·0001
NICU admission	20 599	67·1	20 164	66·0	435	310·3	<0·0001

NICU=neonatal intensive-care unit. *The perinatal mortality ratio was calculated as the number of late fetal deaths (death occurring in a fetus weighing ≥1000 g at birth, or if birthweight was unknown at ≥28 weeks' gestation) plus early neonatal deaths per 1000 livebirths.

Table 2: **Perinatal outcome, stratified by absence or presence of severe maternal outcomes**

	All women (N=314 623)	Women with an SMO (n=3024)
Haemorrhage		
Placenta praevia	1304 (0·4%)	187 (6·2%)
Accreta, increta, or percreta placenta	484 (0·2%)	106 (3·5%)
Abruptio placenta	1082 (0·3%)	186 (6·2%)
Ruptured uterus	316 (0·1%)	131 (4·3%)
Post-partum haemorrhage	4716 (1·5%)	808 (26·7%)
Other obstetric haemorrhage	655 (0·2%)	141 (4·7%)
Infection		
Puerperal endometritis	321 (0·1%)	49 (1·6%)
Pyelonephritis	542 (0·2%)	74 (2·5%)
Influenza-like illness	253 (0·1%)	37 (1·2%)
Sepsis and other systemic infections	1216 (0·4%)	229 (7·6%)
Hypertensive disorders		
Chronic hypertension	1362 (0·4%)	118 (3·9%)
Pre-eclampsia (excludes eclampsia)	7001 (2·2%)	493 (16·3%)
Eclampsia	1008 (0·3%)	291 (9·6%)
Abortion and ectopic pregnancy*		
Abortion-related haemorrhage	Not applicable*	280 (9·3%)
Abortion-related infection	Not applicable*	63 (2·1%)
Ectopic pregnancy	Not applicable*	121 (4·0%)
Other complications or diseases		
HIV-positive, AIDS, or HIV wasting syndrome	1326 (0·4%)	47 (1·6%)
Severe anaemia	5015 (1·6%)	1039 (34·4%)
Malaria or dengue	461 (0·2%)	145 (4·8%)
Embolic disease†	55 (0·0%)	26 (0·9%)
Cancer	56 (0·0%)	14 (0·5%)
Heart disease	513 (0·2%)	84 (2·8%)
Lung disease	405 (0·1%)	117 (3·9%)
Renal disease	340 (0·1%)	78 (2·6%)
Hepatic disease	506 (0·2%)	116 (3·8%)
Coincidental disorders	714 (0·2%)	91 (3·0%)
Other disorder leading to organ dysfunction	188 (0·1%)	188 (6·2%)

SMO=severe maternal outcome (ie, maternal near miss or maternal death). *Women who had an abortion and ectopic pregnancy were only included in the study if they had an SMO. †Thromboembolism, amniotic embolism, or air embolism.

Table 3: **Frequency of potentially life-threatening disorders**

Results

Between May 1, 2010, and Dec 31, 2011, we included 314 623 women attending 357 health facilities in 29 countries (figure 2). Most health facilities were located in urban or periurban areas and 132 (37%) were tertiary hospitals (further details of the health facilities are contained in the appendix). The mean period of data collection in each facility was 89 days (SD 21).

Compared with women without an SMO, women with an SMO were more often older than 35 years, multiparous, with a partner, and had less than 5 years of education and had undergone a previous caesarean section (table 1). Women with an SMO had a higher rate of induced labour than did women without an SMO (13·1% with an SMO *vs* 10·5% without an SMO) and caesarean section without labour (33·3% *vs* 12·1%). The overall rate of caesarean section was 28·6% compared with 62·5% for women with an SMO. Proportionally fewer SMOs were reported in women without partners (ie, single, divorced, separated, or widowed) in countries with very high MMRs (appendix). The perinatal mortality ratio in women with SMOs was nearly 15 times higher than it was for women without SMOs (table 2). Other adverse perinatal outcomes, including rates of preterm birth and admission to neonatal intensive care units, were also substantially increased in women with SMOs.

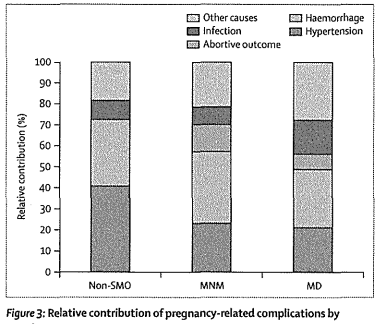

Figure 3: **Relative contribution of pregnancy-related complications by severity group**

Non-SMO=women without severe maternal outcomes. MNM=maternal near miss. MD=maternal deaths.

	Women	Proportion of all women (N=314 623)	Proportion of women with an SMO (n=3024)
Cardiovascular dysfunction	1495	0·5%	49·4%
Respiratory dysfunction	920	0·3%	30·4%
Coagulation or haematological dysfunction	832	0·3%	27·5%
Uterine dysfunction or hysterectomy	473	0·2%	15·6%
Neurological dysfunction	341	0·1%	11·3%
Hepatic dysfunction	310	0·1%	10·3%
Renal dysfunction	281	0·1%	9·3%
Unspecified organ dysfunction	23	0%	0·8%
Any organ dysfunction	3024	1·0%	100%

*Identified by presence of life-threatening disorders (markers of organ dysfunction) listed in the appendix.

Table 4: **Frequency of organ dysfunction related to pregnancy***

Post-partum haemorrhage and pre-eclampsia or eclampsia were the two most frequent obstetric complications noted in women with SMO (table 3). Figure 3 shows the relative contribution of key groups of complications according to the maternal outcome (we excluded severe anaemia post-hoc because of a very high prevalence that distorted the distributions). Cardiovascular, respiratory, and coagulation disorders were the most frequent organ dysfunctions in women with SMO (table 4). In general, SMO prevalence increased as level of maternal mortality increased (table 5). Women with SMO in countries with a low MMR had a reduced severity of illness compared with other groups. Overall, 2164 (9·5%) of 22 840 women with potentially life-threatening disorders were referred to study centres from other hospitals. Mean length of hospital stay for all women was 2·84 days (SD 2·74). Women with an SMO had a mean hospital stay of 4·86 days (4·44), compared with 2·82 days (2·71) for women without an SMO (p=0·0146).

We noted a high coverage of maternal health interventions in health facilities in the different country groups (table 6, appendix). However, 550 (18%) of 3024 women with an SMO did not receive at least one of the indicated essential interventions (eg, magnesium sulphate in the case of eclampsia). Overall, we regarded 638 of these occurrences in women with an SMO as missed opportunities. Risk of mortality was not increased in women with missed opportunities in the SMO group (103 deaths in 550 women with missed opportunities *vs* 383 deaths in 2474 women without missed opportunities; cluster-effect adjusted odds ratio 1·26 [95% CI 0·81–1·97], p=0·3296).

The MSI model had good accuracy for prediction of maternal death in women with markers of organ dysfunction (AUROC for the MSI-derived estimates 0·826 [95% CI 0·802–0·851]). The observed mortality in countries with a moderate MMR was similar to the predicted (SMR 0·91 [95% CI 0·62–1·32]). The MSI receiver operating characteristic curves, data for the capacity of health facilities to assess the markers of severity, an estimation of the level of underestimation in under-resourced settings and further methodological details are shown in the appendix.

Observed mortality in health facilities located in countries with high and very-high MMRs was 2–3-times higher than that expected for the level of assessed severity (figure 4). The appendix includes a breakdown of selected maternal health care indicators by country.

	Low MMR	Moderate MMR	High MMR	Very high MMR	Overall
Countries	2	15	5	7	29
Hospitals	11	156	68	122	357
Women	7487	135795	70753	100588	314623
Livebirths	7459	134545	68565	96202	306771
Women with complications	1164	9969	5452	6430	23015
Women with severe maternal outcomes	35	873	591	1525	3024
Maternal near-miss cases	35	824	422	1257	2538
Maternal deaths	0	49	169	268	486
Indicators					
Ratio of potentially life-threatening complications per 100 livebirths*	15·6	7·4	8·0	6·7	7·5
Maternal near-miss ratio†	4·7	6·1	6·2	13·1	8·3
Severe maternal outcome ratio‡	4·7	6·5	8·6	15·9	9·9
Intrahospital maternal mortality ratio§	0·0	36	246	279	158
Maternal severity score¶	1·5 (0·9)	2·3 (2·5)	3·0 (2·9)	1·9 (1·8)	2·2 (2·3)
Maternal severity index‖	2·3% (9·3)	6·2% (18·3)	13·5% (25·0)	5·4% (15·8)	7·2% (18·8)

Data are n or mean (SD). SMO=severe maternal outcome (ie, maternal near miss or maternal death). *Number of women with potentially life-threatening disorders per 100 livebirths. †Number of maternal near-miss cases per 1000 livebirths. ‡Number of women with severe maternal outcomes per 1000 livebirths. §Limited to 7 days after pregnancy termination, per 100 000 livebirths. ¶Total number of markers of organ dysfunction (ie, life-threatening disorders listed in the appendix) in women with SMO (between-group difference p=0·0001). ‖Model-estimated probability of maternal deaths in women with SMO (between-group difference p<0·0001).

Table 5: **Frequency and severity of complications related to pregnancy**

	Low MMR countries	Moderate MMR countries	High MMR countries	Very high MMR countries	Overall	p value
Coverage of prophylactic oxytocin	6123/7487 (81·8%)	122 326/135 337 (90·4%)	62 018/70 364 (88·1%)	91 208/99 471 (91·7%)	281 675/312 659 (90·1%)	0·4902
Coverage of therapeutic oxytocin*	528/648 (81·5%)	1758/1996 (88·1%)	601/712 (84·4%)	1164/1360 (85·6%)	4051/4716 (85·9%)	0·4471
Coverage of magnesium sulphate for eclampsia	3/4 (75·0%)	192/216 (88·9%)	230/286 (80·4%)	439/502 (87·5%)	864/1008 (85·7%)	0·2694
Coverage of prophylactic antibiotics for caesarean section	553/1547 (35·7%)	49 126/53 572 (91·7%)	15 727/18 975 (82·9%)	12 719/15 421 (82·5%)	78 125/89 515 (87·3%)	<0·0001
Coverage of parenteral antibiotics for sepsis	47/68 (69·1%)	475/562 (84·5%)	214/342 (62·6%)	218/244 (89·3%)	954/1216 (78·5%)	0·0453

Coverage indicators were calculated as the proportion of the target population who received the intervention. MMR=maternal mortality ratio. *For post-partum haemorrhage.

Table 6: **Coverage of key interventions by country group**

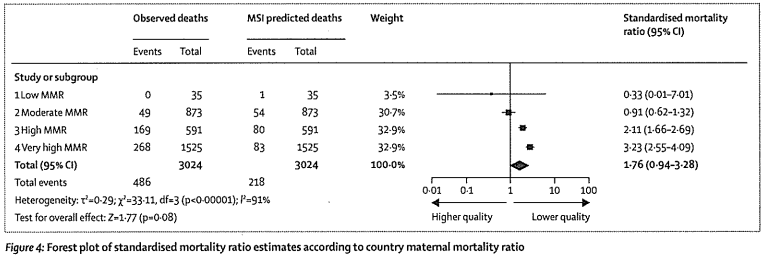

Figure 4: **Forest plot of standardised mortality ratio estimates according to country maternal mortality ratio**

Discussion

About 7% of our study population of 314 623 women had potentially life-threatening disorders and about 1% developed an SMO. Despite the high coverage of interventions regarded as essential to prevent and treat key causes of maternal deaths in participating facilities, care performance and the outcomes of women overall were very variable. In our large network of health facilities, only a small proportion of women with an SMO did not receive the recommended essential intervention. The MSI was validated in this multicountry population.

To our knowledge, our investigation is the largest study to date assessing management of severe complications and the prevalence of maternal near miss by use of

Panel: **Research in context**

Systematic review

The WHO Department of Reproductive Health and Research periodically reviews studies of severe maternal morbidity and maternal near miss. In two published systematic reviews,[10,12] a growing interest was observed in the application of the idea of maternal near miss as an adjunct to maternal mortality reviews and assessments. However, the published literature has notable variation in the criteria used to identify maternal near-miss cases. This inconsistency triggered WHO to develop a standard set of criteria for identification of maternal near-miss cases, which focus on the recognition of organ dysfunction through clinical, laboratory, or management markers.[13]

Interpretation

In this study, the WHO criteria for identification of maternal near-miss cases were used with a criterion-based clinical audit approach to assess the quality of maternal health care in a large network of health facilities from 29 countries. This study improves on the methods previously used to assess the performance of maternal health care by providing external validation to the maternal severity index, which is a model-derived estimate of the probability of maternal mortality.[15] The findings provide information that can enable more objective assessment and benchmarking of the management of severe maternal morbidity. They also draw attention to the role of the so-called essential interventions for the reduction of maternal mortality. If substantial reductions in maternal mortality are to be achieved, universal coverage of life-saving interventions must be matched with comprehensive emergency care and overall improvements in the quality of maternal health care.

standardised definitions in several countries (panel). We were able to capture about 0·7% of the maternal deaths that occurred during a 3-month period worldwide. However, despite several procedures adopted to ensure appropriate study implementation and high quality data, some limitations need to be considered. The first limitation was the size of the WHOMCS and the number of personnel involved (>1500 collaborators). With a study of this size, standardisation of processes is a challenging task, but the different mechanisms we used (such as training, use of a visual check of the data collection forms before data entry, automated queries, double-checking of selected medical records, and thorough audit of unclear cases, especially maternal deaths) was expected to have reduced methodological heterogeneity and increased data quality as much as possible. The primary data source was routine hospital records, which might not be ideal in many settings. To address this issue, several facilities adopted the study data collection form as a platform for their medical records. In cases of unclear or missing information, medical staff were asked to complete the information in the record. To keep the data collection burden to a minimum and ensure feasibility, we only collected short-term (maximum 7 days after the end of pregnancy) in-hospital maternal and perinatal morbidity and mortality data. Some survivors might thus have died within the remaining puerperal and neonatal period. Moreover, in settings where basic laboratory tests were not available, underidentification of near-miss cases and underestimation of severity might have occurred. Unfortunately, in such settings, many women with unrecognised organ dysfunctions might die because of an absence of appropriate life support, worsening the ratio of maternal deaths to maternal near-miss cases. Another limitation was that the study design did not allow us to assess the adequacy of management of first and second stage of labour (eg, we did not assess the monitoring of labour and maternal-fetal wellbeing and the use of labour augmentation in case of delays or expedited delivery in case of fetal distress) and hence we report no data for the prevalence of prolonged or obstructed labour. Finally, the WHOMCS was done mainly in secondary and tertiary facilities, and these data might not be representative of maternal outcomes and coverage of essential interventions in smaller facilities or in the community.

Several factors potentially explain the mismatch between high coverage of essential interventions and the substantial variation in health outcomes noted in our study. The high coverage of essential interventions suggests that these interventions are available and used in most health facilities that took part in this study. Delays in implementation of these interventions or interventions poorly implemented could explain part of the excessive mortality and morbidity noted in some settings. Verticalisation of care (ie, application of single elements of care in disconnection of comprehensive care) could be an issue: other elements of care and quality might have a strong role in survival of severe maternal morbidity. In the context of post-partum haemorrhage, prophylactic and therapeutic uterotonics are essential but shock management and prompt surgical care are also vital. Magnesium sulphate is fundamental to the management of eclampsia, but other aspects of care (such as predelivery stabilisation, severe hypertension management, or airway management for adequate oxygenation and prevention of aspiration pneumonia) are also essential. The role of infection needs to be emphasised: prevalence of infection increased in our study as case severity increased (figure 3). Furthermore, prevalence of sepsis and other systemic infections was more than four times the prevalence of puerperal endometritis (table 3). This difference suggests that prevention, early identification, and appropriate management of secondary infections (eg, postoperative infection or aspiration pneumonia) and other non-obstetric infections should be regarded as a high priority. Another issue is that, in countries with a very high MMR, assessment of severity is often incomplete: severity is apparently underestimated because of a lack of information related to organ dysfunction. In settings where important constraints in the assessment of severity exist, the SMR tends to be somewhat inflated (SMR >3·0), suggesting not only excessive mortality but also underestimation of severity. Poor assessment of severity might contribute to delays in the implementation of effective interventions and poor clinical management. Health systems issues (such as referral processes), undernutrition, pre-existing moderate-to-severe anaemia and other factors could also have contributed to worse health outcomes.

In view of our study characteristics, our findings should not be regarded as representative of all countries, but indicative of the situation in a large sample of health facilities. The situation in the communities or in peripheral health facilities is likely to be different, especially in terms of coverage of essential interventions. The coverage of facility-based care in a specific geographical area might influence the frequency of complications reported at the facility level (eg, in countries with high coverage of births taking place in health-care facilities, the sample might have been diluted with low-risk cases). The external validation of the MSI model in this database encourages its use in other populations, and consideration should be given to the previously mentioned additional information provided by very high SMRs (>3·0). The MSI (and the derived SMR) can be used to monitor and assess the performance of health facilities providing care to women with complications related to pregnancy. The MSI allows adjustment for severity, improvements to comparisons between health facilities, and progress tracking over time. Finally, the MSI can assist health managers and policy makers in the decision-making process of allocation of resources: in a health system, facilities with poor performance and high burden of complications related to pregnancy can be objectively identified and clear prioritisation of investments can be made; in a single health facility, the MSI can be used to compare the facility performance of care against a benchmark and to track progress over time.

No quick fix exists to reduce maternal mortality. In our study, a high coverage of essential interventions did not imply reduced maternal mortality in the hospitals studied. If substantial reductions in maternal mortality are to be achieved, universal coverage of life-saving interventions needs to be matched with comprehensive emergency care and overall improvements in the quality of maternal health care.

Contributors

This project is the result of an international collaborative effort by a large group of institutions and researchers members of the WHO Multicountry Survey on Maternal and Newborn Health (WHOMCS) research group. JPS, JV, and AMG drafted the report on behalf of the WHOMCS Research Group with substantial contributions from BF, CCu, DG, EO-P, GC, JGC, KJ, LC, ML, MR, PL, RM, RP, and ZQ (alphabetical order). All members of the WHOMCS Research Group read and approved the final manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

The WHO Multicountry Survey on Maternal and Newborn Health is a research project implemented by the WHO in a global network of health facilities between 2010 and 2011. This project is part of the WHO response to the United Nations Secretary-General's call for action to improve women's and children's health around the world. WHO is grateful to the extensive network of institutions and individuals who contributed to the project design and implementation, including researchers, study coordinators, data collectors, data clerks, and other partners including the staff from the Ministries of Health and WHO offices. All listed authors are members of the WHOMCS Research Group. The WHOMCS Research Group is grateful to Maria Helena de Sousa (CEMICAMP, Campinas, Brazil) and Armando Seuc (WHO, Geneva, Switzerland) for their advice on statistical methods for analysis of complex samples and surveys.

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For more on the **Multicountry Survey on Maternal and Newborn Health and derivatives** see http://www.who.int/reproductivehealth/topics/maternal_perinatal/nearmiss

Use of antenatal corticosteroids and tocolytic drugs in preterm births in 29 countries: an analysis of the WHO Multicountry Survey on Maternal and Newborn Health

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Summary

Background Despite the global burden of morbidity and mortality associated with preterm birth, little evidence is available for use of antenatal corticosteroids and tocolytic drugs in preterm births in low-income and middle-income countries. We analysed data from the WHO Multicountry Survey on Maternal and Newborn Health (WHOMCS) to assess coverage for these interventions in preterm deliveries.

Methods WHOMCS is a facility-based, cross-sectional survey database of birth outcomes in 359 facilities in 29 countries, with data collected prospectively from May 1, 2010, to Dec 31, 2011. For this analysis, we included deliveries after 22 weeks' gestation and we excluded births that occurred outside a facility or quicker than 3 h after arrival. We calculated use of antenatal corticosteroids in women who gave birth between 26 and 34 weeks' gestation, when antenatal corticosteroids are known to be most beneficial. We also calculated use in women at 22–25 weeks' and 34–36 weeks' gestation. We assessed tocolytic drug use, with and without antenatal corticosteroids, in spontaneous, uncomplicated preterm deliveries at 26–34 weeks' gestation.

Findings Of 303 842 recorded deliveries after 22 weeks' gestation, 17 705 (6%) were preterm. 3900 (52%) of 7547 women who gave birth at 26–34 weeks' gestation, 94 (19%) of 497 women who gave birth at 22–25 weeks' gestation, and 2276 (24%) of 9661 women who gave birth at 35–36 weeks' gestation received antenatal corticosteroids. Rates of antenatal corticosteroid use varied between countries (median 54%, range 16–91%; IQR 30–68%). Of 4677 women who were potentially eligible for tocolysis drugs, 1276 (27%) were treated with bed rest or hydration and 2248 (48%) received no treatment. β-agonists alone (n=346, 7%) were the most frequently used tocolytic drug. Only 848 (18%) of potentially eligible women received both a tocolytic drug and antenatal corticosteroids.

Interpretation Use of interventions was generally poor, despite evidence for their benefit for newborn babies. A substantial proportion of antenatal corticosteroid use occurred at gestational ages at which benefit is controversial, and use of less effective or potentially harmful tocolytic drugs was common. Implementation research and contextualised health policies are needed to improve drug availability and increase compliance with best obstetric practice.

Funding UNDP–UNFPA–UNICEF–WHO–World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP); WHO; USAID; Ministry of Health, Labour and Welfare of Japan; Gynuity Health Projects.

Introduction

More than 15 million infants are born preterm every year and preterm birth is the largest cause of death among newborn babies (age up to 28 days) and the second largest cause of death in children younger than 5 years.[1] More than 60% of preterm deliveries occur in Africa and Asia. The deleterious effects of preterm delivery on newborn babies can be mitigated through appropriate use of proven interventions such as antenatal corticosteroids for fetal lung maturation (along with other benefits)[2] and tocolytic drugs to delay delivery and potentiate the effects of antenatal corticosteroids or allow transfer to a higher-level facility before delivery.[3]

Injections of corticosteroids before delivery to induce fetal lung maturation and thereby prevent newborn morbidity and mortality has been comprehensively studied for nearly four decades.[4] The most recent Cochrane review (2006) for use of antenatal corticosteroids in women with preterm delivery included 21 randomised controlled trials of 3885 women and 4269 babies.[2] Investigators concluded that antenatal corticosteroid use was associated with an overall 31% reduction in neonatal deaths, and significant reductions in risks of respiratory distress syndrome (34%), cerebroventricular haemorrhage (46%), necrotising enterocolitis (54%), need for respiratory support or intensive-care admission (20%), and systemic infections in the first 48 h of life (44%).

Lancet 2014; 384: 1869–77

Published Online August 13, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60580-8

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Antenatal corticosteroids were effective when given from 26 weeks' to 34 weeks' plus 6 days gestation (even if given less than 24 h before delivery) and did not increase risk of maternal death, chorioamnionitis, or puerperal sepsis. A meta-analysis of the four randomised controlled trials for antenatal corticosteroids for preterm births in middle-income countries suggested that the reduction in mortality might be greater in these countries than in high-income countries.[5] Benefit of antenatal corticosteroids outside this gestational age range is controversial; however, observational evidence suggests effectiveness when given between 22 weeks' and 26 weeks' gestation,[6] and investigators of one trial reported that antenatal betamethasone given to women pregnant with term infants reduced neonatal respiratory distress and admission to neonatal special-care units in newborn babies born by elective caesarean section.[7] Despite the global burden of newborn morbidity and mortality related to preterm births, uptake of antenatal corticosteroids worldwide has been poor—the Bellagio Child Survival Study group[8] estimated antenatal corticosteroid coverage in 2000 to be just 5% for the 42 countries that had 90% of the world's under-5 deaths. Recent data for worldwide use of antenatal corticosteroids are not available.

Spontaneous preterm labour causes 40–45% of preterm births.[9] Tocolytic drugs (such as β-agonists, calcium-channel blockers, and oxytocin antagonists) can be used as temporising measures to inhibit labour progression for up to 7 days.[10–12] Use of tocolytic drugs alone has not been shown to reduce perinatal mortality (although trials have been underpowered for this outcome).[3] However, use of the drugs to delay delivery is recommended to permit transfer to a higher-level facility and to potentiate the effects of corticosteroids (and hence should be used in conjunction with antenatal corticosteroids).[11,12] We did not find any published reports on patterns of tocolytic drug use in preterm labour in low-income and middle-income countries, despite its importance in the management of preterm birth.

We did an analysis of the WHO Multicountry Survey of Maternal and Newborn Health (WHOMCS) dataset for more than 314 000 facility-based deliveries in 29 countries. We aimed to describe patterns of use of antenatal corticosteroids in preterm deliveries and assess the use of tocolytic drugs in spontaneous preterm deliveries.

Methods

Study design and participants

WHOMCS was a cross-sectional, facility-based survey of deliveries between May 1, 2010, and Dec 31, 2011. WHOMCS aimed to characterise severe maternal, perinatal, and neonatal morbidity for a worldwide network of health facilities, with particular focus on WHO maternal near-miss indicators.[13] Methodological details for WHOMCS have been described elsewhere.[13,14] Investigators used a stratified, multistage cluster sampling approach to obtain a global sample of countries from Africa, Asia, Latin America, and the Middle East. Within each country, the capital city was sampled, along with two randomly selected provinces (probability proportional to population). From these areas, seven facilities that had more than 1000 deliveries per year and the capacity to do caesarean sections were randomly selected (if fewer than seven facilities were available, then all were selected). All facilities that were chosen agreed to participate. Data were collected for 2 months in institutions with 6000 or more deliveries every year and for 3 months in institutions with fewer than 6000 deliveries every year. When facilities expected fewer than 3000 deliveries, the data collection period was extended to 4 months.

Study participants were all women who gave birth in participating facilities and women with a severe maternal outcome (death or near-miss) associated with pregnancy, childbirth, or puerperium. Data were obtained prospectively, from time of presentation at the facility until discharge or 7 days post partum (whichever was first). Maternal or perinatal adverse outcomes that occurred after discharge or day 7 or during a post-partum referral were not included. Data collectors reviewed medical records and abstracted de-identified data from records into the individual data form at the time of discharge, transfer, or death. An institutional data form about available obstetric and newborn services was completed in consultation with the head of the department of obstetrics for each facility. Overall, 359 facilities in 29 countries participated in WHOMCS, and data from 314 623 women were recorded. For the purposes of comparison, we defined high-income countries (Japan and Qatar) and low-income and middle-income countries (the remaining 27 countries) according to the World Bank's classification for income group's WHOMCS was approved by the WHO Ethics Review Committee and relevant ethics clearance bodies in participating countries. All authors had access to the WHO Multicountry Survey database; JPV, JPS, and AMG were responsible for the decision to submit the manuscript for publication.

Procedures

WHOMCS captured information about a range of maternal sociodemographic, medical, and obstetric characteristics and outcomes for mothers and newborn babies. The gestational age was recorded in completed weeks on the basis of best available obstetric estimate; the method of estimation was not recorded. Preterm births were defined as infants born before 37 weeks of gestation. The use of antenatal corticosteroids in preterm births was recorded; however, the type, timing, number of doses, and dosing schedule was not. The use of five drug classes as tocolytic drugs for preterm labour was also recorded—β-agonists (eg, terbutaline, ritodrine), non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase (COX) inhibitors (eg, indometacin), calcium-channel blockers (eg, nifedipine), oxytocin antagonists (eg, atosiban), and magnesium sulphate. Use

	Births at 22–25 weeks' gestation (n=497)			Births at 26–34 weeks' gestation (n=7547)			Births at 35–36 weeks' gestation (n=9661)		
	All deliveries	Spontaneous deliveries*†	Provider-initiated deliveries*‡	All deliveries	Spontaneous deliveries†§	Provider-initiated deliveries‡§	All deliveries	Spontaneous deliveries† ¶	Provider-initiated deliveries‡¶
Did not receive antenatal corticosteroids	362 (73%)	235 (71%)	112 (77%)	3373 (45%)	2190 (45%)	1163 (45%)	6934 (72%)	5029 (74%)	1894 (67%)
Received antenatal corticosteroids	94 (19%)	69 (21%)	25 (17%)	3900 (52%)	2522 (51%)	1374 (53%)	2276 (24%)	1440 (21%)	827 (29%)
Use of antenatal corticosteroids not recorded	41 (8%)	25 (8%)	9 (6%)	274 (4%)	194 (4%)	75 (3%)	451 (5%)	349 (5%)	99 (4%)

Columns might not add to 100% because of rounding error. *Does not include 22 women with missing labour status. †Women who delivered preterm after spontaneous onset of labour. ‡Women who delivered preterm after induction of labour or pre-labour delivery (ie, caesarean section). §Does not include 29 women with missing labour status. ¶Does not include 23 women with missing labour status.

Table 1: **Use of antenatal corticosteroids in preterm births (n=17 705 deliveries)**

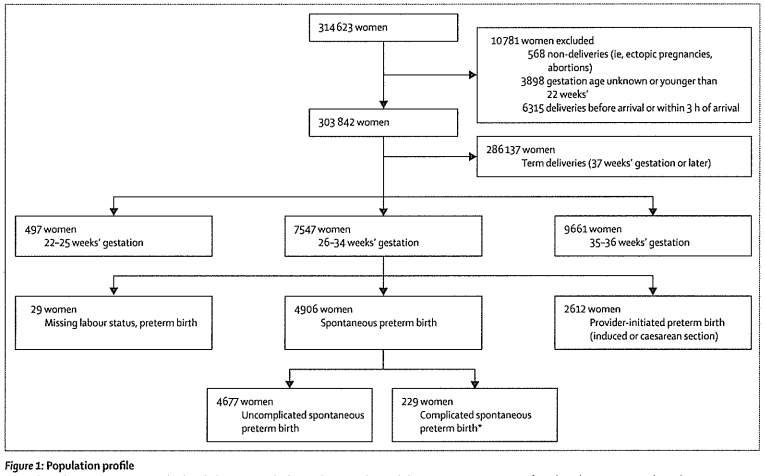

Figure 1: **Population profile**
*Complicated spontaneous preterm birth includes women who have eclampsia, placental abruption, or sepsis (ie, use of tocolytic drugs is contraindicated).

of bed rest, hydration, or no treatment for preterm labour was also recorded.

Statistical analysis

For our analysis, we included pregnancies at or longer than 22 weeks' gestation and excluded abortions, ectopic pregnancies, and pregnancies with unknown gestational age. We excluded deliveries that occurred before a woman's arrival at the facility or within 3 h of arrival because antenatal corticosteroids and tocolytic drugs would be less applicable in these contexts. Preterm deliveries were stratified into three mutually exclusive groups: 22–25 weeks', 26–34 weeks', and 35–36 weeks' gestation. We established the rate of documented antenatal corticosteroid use, both overall and for each country. We identified women who had spontaneous preterm labour at 26–34 weeks' gestation and who did not have a major contraindication to tocolysis (ie, eclampsia, placental abruption, or sepsis). We reported on the documented use of tocolysis treatments, with and without antenatal corticosteroids, in these women. We analysed the crude and adjusted associated effect of maternal, neonatal, and facility characteristics on administration of antenatal corticosteroids by using a multilevel logistic regression model. We also reported their individual effects with odds ratios, and adjusted odds ratios and their 95% CIs. Maternal characteristics recorded were age, marital status, education level, parity, mode of delivery, presence of disorders (ie, chronic hypertension, pre-eclampsia or eclampsia, pyelonephritis, influenza-like illness, other infections or sepsis, HIV/AIDS, and malaria and dengue fever), and number

and sex of fetuses. Facility characteristics recorded were location, level of facility, and level of services available.

We used SPSS version 20.0.0 procedure MULTIPLE IMPUTATION to impute missing values for all model variables (see missing rates in table 1). Overall missing rates were 5% or less for all variables, except for years of education (7·7%). Five imputed datasets were created and used in our model. We converted continuous variables (maternal age, years of education, and parity) to categorical variables after imputation for modelling. We also adjusted our model (using SPSS function GENLINMIXED) for clustering due to hierarchical design of the survey (clustering of women within facilities and facilities within countries was accounted for by use of health facilities as sampling units and countries as strata) with random intercepts at the country and facility level. Because of the weighted sampling design of the WHOMCS, our analysis was self-weighted and no further weighting was applied.

Role of the funding source

JPV, JPS, AMG, MB, and MT are employed by WHO. Some of the funds for the study were from WHO. The non-WHO sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the WHOMCS database. JPV, JPS, and AMG made the decision to submit for publication.

Results

Of 303 842 women included in our analysis, 17 705 (6%) gave birth preterm (figure 1). These deliveries occurred across 359 facilities, mainly in secondary (N=94 740, 31%)

	Coverage of corticosteroids in all deliveries at 26–34 weeks' gestation			Coverage of both tocolytic drugs and antenatal corticosteroids in uncomplicated, spontaneous deliveries at 26–34 weeks' gestation		
	Women who received drugs (n)	Proportion (%)	95% CI*	Women who received drugs (n)	Proportion (%)	95% CI*
Afghanistan	48 (297)	16%	6·6–34·5	2 (207)	1%	0·2–5·2
Angola	33 (129)	26%	12·2–46·0	2 (79)	3%	0·8–7·6
Argentina	136 (185)	74%	62·9–82·0	52 (88)	59%	46·7–70·5
Brazil	86 (288)	30%	13·9–52·9	14 (105)	13%	8·6–20·1
Cambodia	73 (127)	58%	47·2–67·1	9 (75)	12%	3·7–32·8
China	158 (234)	68%	58·7–75·2	52 (125)	42%	30·0–54·2
Democratic Republic of the Congo	26 (159)	16%	6·8–34·4	9 (131)	7%	1·7–23·6
Ecuador	84 (237)	35%	16·8–59·8	34 (148)	23%	9·7–45·3
India	1021 (1481)	69%	60·8–76·1	140 (1102)	13%	7·5–20·7
Japan	30 (52)	58%	38·2–75·0	12 (22)	55%	28·8–78·1
Jordan	19 (21)	91%	78·0–100	5 (8)	63%	29·0–96·1
Kenya	173 (542)	32%	21·3–44·8	23 (334)	7%	3·0–15·0
Lebanon	43 (76)	57%	41·4–70·6	16 (46)	35%	19·9–53·4
Mexico	300 (558)	54%	38·9–68·0	91 (391)	23%	18·9–28·3
Mongolia	108 (156)	69%	62·8–75·0	17 (55)	31%	23·0–40·1
Nepal	46 (236)	20%	5·7–49·1	0 (187)	0	..
Nicaragua	130 (184)	71%	63·8–76·7	56 (92)	61%	45·0–74·7
Niger	12 (60)	20%	7·5–43·7	2 (42)	5%	1·2–17·4
Nigeria	109 (367)	30%	19·7–42·1	27 (188)	14%	5·9–31·1
Occupied Palestinian territory	22 (25)	88%	75·3–100	4 (4)	100%	..
Pakistan	250 (398)	63%	53·3–71·4	37 (195)	19%	9·6–34·0
Paraguay	68 (99)	69%	60·3–76·0	28 (56)	50%	43·4–56·6
Peru	302 (403)	75%	67·1–81·4	78 (183)	43%	30·9–55·2
Philippines	120 (256)	47%	37·0–57·0	33 (193)	17%	10·5–26·6
Qatar	9 (29)	31%	14·2–47·8	1 (18)	6%	0·16·2
Sri Lanka	287 (439)	65%	56·5–73·3	47 (220)	21%	12·9–33·3
Thailand	108 (244)	44%	34·6–54·3	44 (172)	26%	18·8–33·8
Uganda	41 (154)	27%	19·3–35·5	0 (110)	0%	..
Vietnam	58 (111)	52%	40·6–63·6	13 (101)	13%	5·1–29·1
Total	3900 (7547)	52%	47·5–55·8	848 (4677)	18·1%	15·4–21·2

*95% CIs are adjusted for hierarchical survey design.

Table 2: **Coverage of antenatal corticosteroids and tocolytic drugs in countries studied**

	Received antenatal corticosteroids (n=3900)	Did not receive antenatal corticosteroids (n=3373)	Odds ratio* (95% CI)	Adjusted odds ratio† (95% CI)
Maternal age				
Younger than 20 years	332 (9%)	437 (13·0%)	0·62 (0·50–0·77)	0·70 (0·57–0·86)
20–35 years	3116 (80%)	2547 (75·5%)	Ref	Ref
Older than 35 years	443 (11%)	379 (11·2%)	0·96 (0·78–1·17)	0·95 (0·76–1·20)
Data missing	9 (<1%)	10 (<1%)	..	..
Marital status				
Married	378 (10%)	391 (12%)	0·82 (0·60–1·11)	1·25 (0·98–1·61)
Not married	3495 (90%)	2950 (88%)	Ref	Ref
Data missing	27 (1%)	32 (1%)	..	..
Years of education				
0 years	573 (15%)	603 (18%)	0·64 (0·41–0·99	0·84 (0·63–1·11)
1–6 years	576 (15%)	482 (14%)	0·8 (0·60–1·08)	0·83 (0·69–0·99)
7–9 years	723 (19%)	660 (20%)	0·74 (0·55–0·98)	0·87 (0·69–1·10)
10–12 years	1141 (29%)	875 (26%)	0·88 (0·69–1·12)	0·96 (0·80–1·15)
More than 12 years	584 (15%)	392 (12%)	Ref	Ref
Data missing	303 (8%)	361 (11%)	..	..
Parity				
0	1811 (46%)	1448 (43%)	1·06 (0·95–1·19)	1·20 (1·07–1·35)
1–2 children	1580 (41%)	1343 (40%)	Ref	Ref
More than 2 children	508 (13%)	577 (17%)	0·75 (0·61–0·91)	1·04 (0·85–1·27)
Data missing	1 (<1%)	5 (<1%)	..	..
Mode of delivery				
Vaginal delivery	2033 (52%)	2286 (68%)	Ref	Ref
Intrapartum caesarean section	874 (22%)	574 (17%)	1·71 (1·34–2·18)	1·51 (1·13–2·02)
No-labour caesarean section	984 (25%)	488 (15%)	2·27 (1·77–2·90)	2·13 (1·69–2·67)
Data missing	9 (<1%)	25 (1%)	..	..
Maternal disorders				
Chronic hypertension	114 (3%)	64 (2%)	1·56 (1·01–2·41)	1·14 (0·83–1·57)
Pre-eclampsia or eclampsia	714 (18%)	441 (13%)	1·49 (1·22–1·82)	1·14 (0·89–1·46)
Pyelonephritis	23 (1%)	9 (<1%)	2·22 (1·16–4·23)	1·90 (1·07–3·37)
Influenza-like illness	20 (1%)	7 (<1%)	2·25 (1·03–5·98)	1·56 (0·92–2·63)
Other systemic infections or sepsis	85 (2%)	61 (2%)	1·21 (0·81–1·80)	1·28 (0·61–2·69)
HIV/AIDS or HIV wasting syndrome	21 (1%)	28 (1%)	0·65 (0·31–1·37)	1·59 (0·73–3·44)
Malaria or dengue fever	16 (<1%)	27 (1%)	0·51 (0·24–1·11)	0·90 (0·35–2·26)
Sex of infant				
Female	1796 (46·1%)	1592 (47%)	0·93 (0·85–1·03)	0·98 (0·90–1·06)
Male	2096 (53·7%)	1736 (52%)	Ref	Ref
Data missing	8 (0·2%)	45 (1%)	..	..
Number of newborn babies				
One (singleton pregnancy)	3574 (92%	3153 (94%)	Ref	Ref
Two (twin pregnancy)	296 (8%)	197 (6%)	1·33 (1·08–1·63)	3·59 (1·15–11·24)
Three or more (higher-order multiple pregnancy)	29 (1%)	6 (<1%)	4·26 (1·85–9·84)	1·28 (1·03–1·60)
Missing data	1 (<1%)	17 (1%)	..	..
Location‡				
Urban	3483 (89%)	2762 (82%)	Ref	Ref
Peri-urban	162 (4%)	358 (11%)	0·36 (0·17–0·77)	0·79 (0·58–1·07)
Rural	57 (2%)	96 (3%)	0·47 (0·29–0·77)	0·88 (0·77–1·01)
Data missing	198 (5%)	157 (5%)	..	..

(Table 3 continues on next page)

	Received antenatal corticosteroids (n=3900)	Did not receive antenatal corticosteroids n=3373)	Odds ratio* (95% CI)	Adjusted odds ratio† (95% CI)
(Continued from previous page)				
Level of facility‡				
Primary	52 (1%)	82 (2%)	0·41 (0·22–0·78)	0·79 (0·52–1·22)
Secondary	663 (17%)	969 (29%)	0·45 (0·30–0·66)	0·93 (0·69–1·26)
Tertiary	2677 (69%)	1743 (52%)	Ref	Ref
Other referral level	309 (8%)	383 (11%)	0·53 (0·26–1·05)	1·03 (0·82–1·29)
Data missing	199 (5%)	196 (6%)	..	..

Columns might not add to 100% because of rounding error. 274 women had information missing on receipt of antenatal corticosteroids and are not included. Ref=reference comparator group. *Calculation of crude odds ratios adjusted for clustering due to survey design only. †Multilevel logistic regression model adjusted for maternal characteristics (age, marital status, education, parity, and mode of delivery), maternal disorders (chronic hypertension, pre-eclampsia or eclampsia, pyelonephritis, influenza-like illness, other infections or sepsis, HIV/AIDS, malaria, and dengue fever), infant characteristics (sex and number of fetuses), and facility characteristics (location and level of facility, provision of care free of charge at facility, and level of services available at facility), as well as clustering due to survey design. ‡As reported by head of obstetrics department or facility.

Table 3: Maternal and neonatal infant characteristics associated with use of antenatal corticosteroids at 26–34 weeks' gestation (n=7273)

See Online for appendix

	Number of women (%)
Women receiving drugs for tocolysis	970 (21%)
Calcium-channel blocker only	271 (6%)
Oxytocin antagonist only	26 (1%)
β-agonists only	346 (7%)
NSAIDs or COX inhibitors only	48 (1%)
Magnesium sulphate only	85 (2%)
More than one drug given*	194 (4%)
No drug given; treated with bed rest and hydration only†	1276 (27%)
No treatment given for tocolysis	2248 (48%)
Data missing	183 (4%)

Data for 4677 deliveries. NSAIDs=non-steroidal anti-inflammatory drugs. COX=cyclo-oxygenase. *Use of two or more tocolytic drugs including those listed. †No documented use of any of the named drugs or treatments.

Table 4: Use of tocolytic drugs in women with uncomplicated, spontaneous preterm deliveries at 26–34 weeks' gestation

and tertiary (N=131835, 43%) facilities, with the rest in primary (N=16611, 6%) and other referral level (N=36460 12%) facilities; data were missing for 8·0% (N=24196) of deliveries. The 7547 women who gave birth at 26–34 weeks' gestation accounted for 2·5% of all deliveries. Of these events, 4906 (65%) women had a spontaneous preterm birth, of which 4677 (95%) were spontaneous preterm births without a major contraindication to tocolysis. Table 1 shows data for antenatal corticosteroid use in the 17705 women who delivered preterm; 766 (4%) had data missing for use of antenatal corticosteroids. Of the women who delivered at 26–34 weeks' gestation, 52% received antenatal corticosteroids (table 1).

When stratified by spontaneous preterm birth or provider-initiated preterm birth (ie, induced labour or a pre-labour caesarean section), antenatal corticosteroid use for women at 26–34 weeks' gestation was similar (χ^2=0·62). When analysed for countries, median antenatal corticosteroid coverage was 54% (range 16–91%, IQR 30–68%; table 2, appendix). Only two countries exceeded 80% use—Jordan (91%) and occupied Palestinian territory (88%)—however, the number of preterm babies in both countries was quite small. Although we did not know the vital status of the fetus at onset of labour, we did a sensitivity analysis by excluding the 1957 women who had stillbirth with signs of maceration (on the assumption that these fetuses were probably not alive at the start of labour). Use of antenatal corticosteroids increased from 52% (n=3900 of 7547) to 56% (n=3836 of 6909) after we excluded these deliveries. Results from the multilevel logistic regression model with multiple imputation (table 3) showed that the adjusted odds of receipt of antenatal corticosteroids were significantly raised in nulliparous women and in both intrapartum caesarean and pre-labour caesarean deliveries. Women with pyelonephritis had raised adjusted odds of antenatal corticosteroid receipt, as did those pregnant with twins and higher-order multiple pregnancies. The adjusted odds of antenatal corticosteroid use were lower in women younger than 20 years and women with 1–6 years of education. The same model without multiple imputation of missing values returned similar results (data not shown), with no change in significance for covariates except for pyelonephritis (not significant in model without multiple imputation; adjusted odds ratio 1·39, 95% CI 0·79–2·43) and influenza (significant in model without multiple imputation; 2·48, 1·56–3·93).

Among the 4677 women with uncomplicated, spontaneous preterm labour who were eligible for tocolytic treatment, almost half received no treatment and a quarter received non-drug treatments (table 4). The most frequently used drugs for tocolysis were β-agonists and calcium-channel blockers. Only 848 (18%) women in this group received a tocolytic drug in

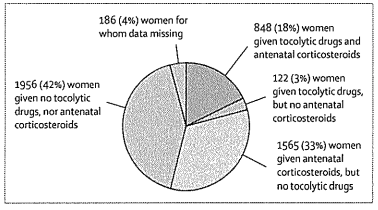

Figure 2: **Use of tocolytic drugs, with and without antenatal corticosteroids, in uncomplicated spontaneous preterm births (26–34 weeks' gestation; n=4677)**
Tocolytic drugs for preterm labour include calcium-channel blockers, oxytocin antagonists, β-agonists, non-steroidal anti-inflammatory drugs and cyclooxygenase inhibitors, and magnesium sulphate. The no tocolytic drug group indicates women treated with bed rest, hydration, or no treatment for preterm labour.

combination with antenatal corticosteroids (figure 2). Most women received neither a tocolytic drug nor antenatal corticosteroids, or antenatal corticosteroids without a tocolysis drug; and a few received tocolysis without concurrent antenatal corticosteroids. At the country level, rates of tocolytic drug use in combination with antenatal corticosteroids were generally low—median rate was 19% (range 0–100; table 2, appendix).

Discussion

Our analysis showed that antenatal corticosteroids and tocolytic drugs were substantially underused in women in whom they would have been beneficial. Use of antenatal corticosteroids at gestational ages at which benefit is more controversial, or use of tocolytic drugs that are ineffective or have higher rates of adverse outcomes, was common and exposed women and their babies to unnecessary risk. Nearly half of eligible women overall did not receive antenatal corticosteroids, and, in many countries, most eligible women did not receive antenatal corticosteroids. Lower-income countries such as Afghanistan, Democratic Republic of the Congo, Nepal, and Niger have particularly high rates of neonatal mortality[15] and low use of antenatal corticosteroids. Antenatal corticosteroid use in the two high-income countries that we assessed (Japan 56% and Qatar 31%) was surprisingly low; however, this finding must be interpreted cautiously because the number of women (52 and 29, respectively) was quite small. Although there are few reports of antenatal corticosteroid use in low-income and middle-income countries (panel), other investigators have noted similarly wide variations—eg, 4–71% of women received corticosteroids in several Latin American countries[16–20] and 9–73% of women in four southeast Asian countries.[21] Of perhaps greater concern is that use of antenatal corticosteroids was low even in preterm births after induction or pre-labour caesarean section; deliveries in which the timing of delivery and need for antenatal corticosteroids could be reasonably anticipated. Although we were unable to explore specific reasons to explain this finding, it suggests that barriers to poor use of antenatal corticosteroids probably extend beyond poor identification of women at risk of preterm delivery. Almost a quarter of women who delivered at 35–36 weeks' gestation received antenatal corticosteroids despite the fact that perinatal morbidity and mortality benefit at these gestational age intervals is somewhat controversial.[2] Uncertainty about gestational age is common in low-income and middle-income countries because antenatal care participation and ultrasound availability can be poor—this uncertainty might have contributed to use of antenatal corticosteroids in gestational ages outside of the 26–34 weeks' gestation range. More appropriate prescribing practices could improve outcomes for the 45% of women at 26–34 weeks' gestation who did not receive antenatal corticosteroids.

The use of tocolytics was generally poor, but it is of great concern that more than a third of eligible women received ineffective treatments for preterm labour. No evidence exists to support the use of bed rest[22] and hydration (if not dehydrated)[23] to prevent preterm delivery, and magnesium sulphate is not effective to delay birth or prevent preterm birth.[24] Haas and colleagues[3] did a systematic review and network meta-analysis for drug treatment options to prevent preterm delivery and reported that prostaglandin inhibitors and calcium-channel blockers have the highest probability of improving neonatal outcomes by delaying delivery and have the lowest maternal side-effects. Prostaglandin inhibitor use is complicated by the risk of oligohydramnios and premature closure of the fetal ductus arteriosus.[25] Nifedipine is comparatively cheaper,[26] is simple to administer, and is the only drug for tocolysis in the WHO Essential Medicines List.[27] β-agonists have similar effectiveness to calcium-channel blockers,[11] but they have higher rates of maternal adverse effects (such as chest pain, breathing difficulties, heart irregularities, headaches, and shaking). In our analysis, β-agonists were the most commonly used effective tocolytic drug, despite the known maternal side-effects, and only 6% of eligible women received calcium-channel blockers. This pattern might be due to historical reasons; however, it shows that changes in tocolytic prescribing practices could improve both maternal and neonatal outcomes. Ideally, women in spontaneous preterm labour between 26 and 24 weeks of gestation who receive tocolytics should recieve antenatal corticosteroids in combination, yet only 15% of eligible women received both treatments and 42% received neither. As far as we know, our data are the first international comparison of tocolytic drug use with antenatal corticosteroids in preterm birth across lower-income countries. Further research on the determinants of tocolytic prescription would help to identify interventions to improve compliance with best practices in preterm labour management.

A 2013 survey by Aleman and colleagues[28] identified several barriers to improved uptake of antenatal

Panel: Research in context

Systematic review

In women at 26–34 weeks' gestation at risk of preterm birth, the efficacy of antenatal corticosteroids to accelerate fetal lung maturation is unquestioned; contributors to a 2006 Cochrane review[2] explored the subject extensively. Similarly, the efficacy and adverse effects of individual tocolytic drugs (such as betamimetics,[19] calcium-channel blockers,[11] oxytocin receptor antagonists,[12] and magnesium sulphate[24]) have been the subject of Cochrane reviews.

Interpretation

Despite the wealth of trial evidence about the efficacy and indications for antenatal corticosteroids and tocolytic drugs in preterm birth, remarkably little data are available for clinical patterns of their use, particularly in low-income and middle-income countries where most of the global burden of preterm-associated neonatal mortality occurs. Our findings provide the first internationally comparable, comprehensive study of prevalence of use for antenatal corticosteroids. We suggest that a substantial amount of preterm-birth-associated newborn morbidity and mortality could be avoided through improvements in the delivery of these known interventions. Intensive efforts to scale up use of antenatal corticosteroids in facility settings are needed.

corticosteroids in four Latin American countries, including corticosteroids not being available at hospitals and primary health centres, fear or doubt among health providers about side-effects, misinformation about correct use, and insufficient personnel. They also reported economic barriers to access, and fear and misinformation among women about antenatal corticosteroids.[28] Although we were unable to identify specific barriers for the use of antenatal corticosteroids and tocolytic drugs, younger women and women with little education were less likely to receive corticosteroids than were others, suggesting social inequalities might be at play.

Our findings have substantial implications for both clinicians and health policy makers. If recognition of preterm labour is to be followed by early antenatal corticosteroids (with or without tocolytic drugs) then drugs should be readily available at the time and place of presentation. We therefore recommend inclusion of dexamethasone or betamethasone or both on national essential medicines lists to improve outcomes for preterm babies. This action would improve access in all health facilities, particularly in lower-level facilities, which are often the point of first contact for women in preterm labour. Additionally, despecialising prescription of antenatal corticosteroids could allow some health professionals (such as emergency doctors and midwives) to give these drugs could reduce delays in access to this life-saving intervention. 2012 WHO guidance for task shifting[29] recommends that the use of midwives to give corticosteroids in preterm labour should be researched rigorously.

In facilities where antenatal corticosteroids and tocolytic drug are available but underused or misused, implementation research, including a deeper understanding of barriers to their use, is needed. Clinical guidelines and education for all health-care workers to recognise and manage preterm labour can reduce barriers to increased use. Interventions to increase demand could also change practice. For example, community mobilisation and provision of antenatal corticosteroids free of charge to all women at risk of preterm labour would not only increase demand, but would also address the socioeconomic inequities in antenatal corticosteroid use and improve coverage in higher-risk subpopulations (such as adolescents and poorly educated mothers).

Some limitations could have affected the results of our analysis. WHOMCS was mainly a study of maternal and perinatal morbidity and mortality, of which preterm birth is an important component, but was not the survey's main aim. The number of countries participating in the multicountry survey was limited by financial constraints; hence, Europe was not sampled. Although robust, the multistage facility sampling design could potentially introduce bias, because women from countries with smaller populations are oversampled compared with women from countries with larger populations. Within the same country, when smaller, lower-level facilities are randomly sampled, complicated deliveries might be under-represented. Conversely, in countries where maternity care is centralised in a few, large facilities (particularly in the capital city) or where such facilities were randomly sampled, complicated deliveries are probably over-represented. These data are probably not representative of smaller facilities and communities not included in the sampling frame; however, we believe it is reasonable to assume that antenatal corticosteroid and tocolytic drug availability is high in large facilities, and that higher-level facilities and coverage rates are probably poorer in lower-level facilities. In some countries, the number of deliveries in lower-level facilities is proportionally greater, thus coverage might still be poor even when the national rate of facility delivery is high. Data for WHOMCS were abstracted from hospital records; in many facilities, these records are suboptimum and use of interventions might not have been documented correctly (particularly those occurring before facility admission). This bias was minimised as much as possible because data collectors consulted with medical staff about missing information; however, some treatment might be undocumented or could have occurred before arrival at the facility, leading to a possible underestimation of coverage. Conversely, failure to recognise preterm births due to poor estimation of gestational age might lead to an overestimate of drug use. Under-recognition of prematurity also probably contributed to the recorded preterm birth rate (5·8%) being lower than was expected based on recent estimates.[1] Fetal status on arrival for delivery, as well as the type, timing, dose, and frequency of antenatal corticosteroids and tocolytic drugs, was not included in WHOMCS, and we were unable to account for all contraindications to these drugs (such as drug allergies, maternal cardiac diseases, and advanced cervical dilatation). A small proportion of antenatal corticosteroid use at 35–36 weeks'

gestation might be attributable to women who were treated earlier than 35 weeks' gestation but who delivered after 35 weeks' during the same admission. Although missing data might have led to a bias in our findings, missing rates were generally low (≤5%) and results from modelling, both with and without multiple imputation, were similar, increasing our confidence that missing values had negligible effect.

Despite the evidence for effectiveness of antenatal corticosteroids and tocolytic drugs in preterm deliveries, their use was highly variable and often poor. A substantial proportion of antenatal corticosteroid use was at extremes of gestational age when benefit is controversial, whereas a significant proportion of mothers of infants at 26–34 weeks' gestation did not receive this life-saving intervention. The use of ineffective, less effective, or potentially harmful treatments for tocolysis was also widespread. Implementation research and contextualised health policies are needed to improve drug availability and compliance with best obstetric practices.

Contributors
JPV and JPS conceptualised the Article and analysis plan. JPV did the analyses, in collaboration with JPS and AMG. All authors contributed to the interpretation of results. JPV drafted the initial report and JPS, AMG, RM, PL, ZQ, GC, ML, BF, TG, JZ, MRT, MB, and MT contributed to the content and revisions.

Declaration of interests
We declare no competing interests.

Acknowledgments
We thank all members of the WHO Multicountry Survey on Maternal and Newborn Health Research Network, including regional and country coordinators, data collection coordinators, facility coordinators, data collectors, and all staff of participating facilities who made the survey possible. JPV is supported by the Australian Postgraduate Award and the A & A Saw Scholarship. This manuscript represents the views of the named authors only.

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PLOS ONE

Risk Factors and Adverse Perinatal Outcomes among Term and Preterm Infants Born Small-for-Gestational-Age: Secondary Analyses of the WHO Multi-Country Survey on Maternal and Newborn Health

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Abstract

Background: Small for gestational age (SGA) is not only a major indicator of perinatal mortality and morbidity, but also the morbidity risks in later in life. We aim to estimate the association between the birth of SGA infants and the risk factors and adverse perinatal outcomes among twenty-nine countries in Africa, Latin America, the Middle East and Asia in 359 health facilities in 2010–11.

Methods: We analysed facility-based, cross-sectional data from the WHO Multi-country Survey on Maternal and Newborn Health. We constructed multilevel logistic regression models with random effects for facilities and countries to estimate the risk factors for SGA infants using country-specific birthweight reference standards in preterm and term delivery, and SGA's association with adverse perinatal outcomes. We compared the risks and adverse perinatal outcomes with appropriate for gestational age (AGA) infants categorized by preterm and term delivery.

Results: A total of 295,829 singleton infants delivered were analysed. The overall prevalence of SGA was highest in Cambodia (18.8%), Nepal (17.9%), the Occupied Palestinian Territory (16.1%), and Japan (16.0%), while the lowest was observed in Afghanistan (4.8%), Uganda (6.6%) and Thailand (9.7%). The risk of preterm SGA infants was significantly higher among nulliparous mothers and mothers with chronic hypertension and preeclampsia/eclampsia (aOR: 2.89; 95% CI: 2.55–3.28) compared with AGA infants. Higher risks of term SGA were observed among sociodemographic factors and women with preeclampsia/eclampsia, anaemia and other medical conditions. Multiparity (> = 3) (AOR: 0.88; 95% CI: 0.83–0.92) was a protective factor for term SGA. The risk of perinatal mortality was significantly higher in preterm SGA deliveries in low to high HDI countries.

Conclusion: Preterm SGA is associated with medical conditions related to preeclampsia, but not with sociodemographic status. Term SGA is associated with sociodemographic status and various medical conditions.

Citation: Ota E, Ganchimeg T, Morisaki N, Vogel JP, Pileggi C, et al. (2014) Risk Factors and Adverse Perinatal Outcomes among Term and Preterm Infants Born Small-for-Gestational-Age: Secondary Analyses of the WHO Multi-Country Survey on Maternal and Newborn Health. PLoS ONE 9(8): e105155. doi:10.1371/journal.pone.0105155

Editor: Cornelis B. Lambalk, VU University Medical Center, Netherlands

Received December 3, 2013; **Accepted** July 21, 2014; **Published** August 13, 2014

Funding: This study is financially supported by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP); the World Health Organization (WHO); the United States Agency for International Development (USAID); the Ministry of Health, Labour and Welfare of Japan, and Gynuity Health Projects. The sponsors had no role in the data collection, analysis, or interpretation of the data, the writing of the report, or the decision to submit for publication. All authors had access to the analysis plan, the outputs of that analysis and could see the data if they wished to do so. All authors participated in the final discussion and approved the submission.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Small for gestational age (SGA) refers to infants whose size and weight is less than the average range for infants of the same gestational age. GA is not only a major indicator of perinatal mortality and morbidity [1,2], but also increases the risk of chronic diseases such as cardiovascular disease and diabetes or developmental outcomes later in life [3,4]. In a UK population-based cohort study from 1997 to 2003, 43% of stillbirths were related to SGA [5]. Among 135 million infants born in low- and middle-income countries (LMICs) in 2010, it is estimated that 29.7 million (22%) were born term-SGA, 10.9 million (8.1%) were born preterm appropriate-for-gestational-age (AGA), and 2.8 million (2.1%) were born preterm-SGA [6]. However, it is a great challenge to define SGA in various ethnic groups in an international comparative study. Based on the secondary analysis using 20 cohort studies for national and regional estimates of SGA babies, 62% of SGA deliveries occurred in India, and 56% occurred in Nepal [7]. This overestimation arose due to the use of the Alexander reference in the analysis, which adapted very high-income country group (US) data from 1991 to low- and middle-income countries. The country-specific birth reference was required to avoid an under- or overestimate of SGA status, especially in low- and middle-income countries. Birthweight references based on neonatal birthweight at each gestational week have been used for nearly 50 years. This type of reference is not so effective under diagnosis in the early gestational weeks, especially for preterm SGA. Therefore, ultrasound-based estimated references of fetal weight are more suitable to overcome this problem. Mikolajczyk developed an ultrasound-based generic global reference to measure fetal weight and birthweight in low-, middle- and high-income settings [8]. Although this country-specific reference has already been used in a previous study to define macrosomia for international comparison [9], our study is the first to use this global reference to define SGA for international comparison.

The cause of SGA is multifactorial, and comprised of maternal, placental, fetal or environmental factors. Identified maternal factors of SGA include demographic variables and medical conditions, such as maternal age [10,11], nulliparity [11,12], cigarette smoking [12–15], short stature [12], caffeine intake [16], low or high maternal body mass index (BMI) [10], hypertension and preeclampsia [11,12,17], psychosocial stress [15], and socioeconomic status, including education [14,17–20]. Conflicting evidence exists for increased [21–23] or decreased [24,25], or unchanged [26,27] neonatal mortality and morbidity rates for preterm SGA compared with preterm AGA. Risk factors, interventions and sequelae for preterm SGA might differ from term SGA. Despite the high prevalence of SGA, only a limited number of studies exist due to a lack of gestational age data, especially in LMICs. Furthermore, few studies have considered risk factors for SGA in preterm and term deliveries compared with preterm AGA [10,23,28]. Therefore, we aimed to explore trends and risk factors associated with SGA and its mortality in preterm and term deliveries across multiple low- to very high- income countries by taking advantage of the WHO Multi-country Survey on Maternal and Newborn Health data, which covers 29 low- to very high-income countries globally.

Methods

This is a secondary data analysis of the WHO Multi-country Survey on Maternal and Newborn Health, which was conducted in 359 health facilities across 29 countries in Africa, Asia, Latin America and the Middle East. Methodological details of this survey have been published elsewhere [29,30]. In brief, a multistage cluster sampling method was used to obtain samples of health facilities in two provinces and each capital city of the 29 randomly selected countries. All women admitted for delivery plus all women with severe maternal outcomes regardless of gestational age were recruited in the study. Individual data on demographics and reproductive characteristics, medical conditions during pregnancy, birth outcomes, and complications were collected from the participants' medical records. Health facility capacity data were obtained, such as the capabilities of essential and comprehensive obstetric and neonatal healthcare services, laboratory tests, and human resources and training. The study was implemented concurrently in 29 countries over two to four months from May 2010 to December 2012.

Study population and statistical analysis

The study population was restricted to pregnancies of at least 28 gestational weeks for comparability of viable gestational age between countries, and singleton births with no congenital malformation. We excluded deliveries with missing data on birthweight, gestational age, and infant gender, as well as pregnancies that lasted less than 22 weeks or more than 42 weeks with congenital malformation.

To overcome the existing deficiency in birthweight references in LMICs, and taking into account birthweight variations across countries, we adopted methodology to generate local (country-specific) fetal weight and birthweight references developed by Mikolajczyk et al. [8].

To generate a country weight-reference standard, first we used the mean birthweight for infants born to married mothers aged 20–34 years with schooling years ≥12, who had no pregnancy complications, and who vaginally delivered singleton infants with no complications at 40 completed weeks of gestation (40 weeks+0 days to 40 weeks+6 days). Next, we based the birthweight (mean and SD) reference on a gestational age of 40 weeks, and we obtained the mean fetal-weight and percentiles across each gestational week for all countries participating in this study. We defined SGA as a birthweight below the 10^{th} percentile, AGA as between the 10^{th} and 90^{th} percentiles and large-for-gestational age (LGA) as above the 90^{th} percentile at the gestational ages of 28 to 41 weeks by infant gender. The study population was restricted to deliveries with a birthweight below the 90^{th} percentile, excluding LGA due to the condition's high risk of adverse birth outcomes.

We considered the following variables as exposures at the individual level and further categorized them as shown in tables: maternal age defined as completed years at the time of delivery; marital status; years of education, parity; presence of chronic hypertension, preeclampsia or eclampsia, severe anaemia with haemoglobin <7 mg/dl, malaria or dengue, HIV or AIDS and other conditions defined as the presence of disease or injury affecting the heart, lungs, liver and kidneys. Additionally, we adjusted our analysis for facility capacity and the human development index (HDI). Facility capacity was used in previous studies and is defined as the total score of essential and additional services provided by health facilities with further categorization into high, medium and low capacity [31]. The human development index (HDI) for each country was adopted from 2012 UN development program estimates [32].

Perinatal outcomes considered in the study were fresh stillbirths (excluding macerated stillbirths), early neonatal death, perinatal death (both fresh stillbirth and early neonatal death) and neonatal near miss [33]. Neonatal near miss is defined as a neonate who survived a life-threatening condition and presented with any of the following conditions: any intubation at birth or anytime within the first week of life, nasal continuous positive airway pressure, surfactant administration, cardiopulmonary resuscitation (cardiac massage), any surgery, or use of any vasoactive drug, anticonvulsants, phototherapy in the first 24 hours, steroids to treat refractory hypoglycaemia, or therapeutic intravenous antibiotics. Early neonatal deaths were defined as intra-hospital deaths that occurred on or before the seventh day after delivery.

Table 1. Birthweight and proportion of SGA by country.

HDI group	Country (by rank)	Total number of deliveries	Birthweight [mean (SD)]	Small for gestational age (SGA)			
				All [n (%)]	Gestational age (weeks) [n (%)]		
					≤32	33–36	37–41
Very high	Japan	3,391	2975.3 (397.8)	543 (16.0)	2 (9.5)	27 (18.1)	514 (15.9)
	Qatar	3,744	3285.8 (477.2)	453 (12.1)	3 (42.8)	15 (10.5)	435 (12.1)
	Argentina	9,416	3320.7 (516.7)	1,239 (13.2)	40 (50.6)	122 (25.4)	1,077 (12.5)
High	Mexico	12,759	3054.3 (508.3)	1,669 (13.1)	69 (31.9)	234 (25.3)	1,366 (11.8)
	Lebanon	3,826	3175.5 (478.7)	384(10.0)	10 (23.8)	32 (14.3)	342 (9.6)
	Peru	14,450	3310.3 (521.8)	2,120 (14.7)	68 (40.9)	208 (31.2)	1,844 (13.5)
	Brazil	6,729	3161.0 (529.5)	964 (14.3)	39 (33.9)	116 (21.7)	809 (13.3)
	Ecuador	9,810	3070.1 (493.3)	1,335 (13.6)	45 (39.1)	121 (23.9)	1,169 (12.7)
	Sri Lanka	17,530	2925.5 (464.6)	2,249 (12.8)	37 (26.8)	194 (17.8)	2,018 (12.4)
Medium	Jordan	1,066	3119.2 (542.6)	127 (11.9)	5 (27.7)	13 (15.3)	109 (11.3)
	China	12,780	3277.5 (468.4)	1,303 (10.2)	17 (17.5)	78 (12.8)	1,208 (10.0)
	Thailand	8,687	3062.1 (467.8)	841 (9.7)	19 (18.8)	68 (9.1)	754 (9.6)
	Mongolia	7,095	3390.1 (502.0)	711 (10.0)	20 (25.6)	43 (16.9)	648 (9.6)
	OPT	884	3221.3 (502.6)	142 (16.1)	4 (44.4)	15 (27.3)	123 (15.0)
	Paraguay	3,492	3276.6 (535.2)	369 (10.6)	13 (36.1)	41 (18.5)	315 (9.7)
	Philippines	10,120	2923.9 (490.4)	1,520 (15.0)	40 (21.6)	139 (24.0)	1,341 (14.3)
	Vietnam	14,803	3185.3 (430.9)	2,141 (14.5)	15 (29.4)	91 (24.5)	2,035 (14.2)
	Nicaragua	6,231	3043.2 (496.3)	755 (12.1)	27 (26.0)	73 (18.2)	655 (11.4)
	India	30,034	2652.3 (494.3)	3,416 (11.4)	95 (11.6)	366 (14.8)	2,955 (11.1)
	Cambodia	4,525	3001.4 (481.2)	852 (18.8)	12 (11.7)	45 (31.0)	795 (18.6)
Low	Kenya	18,676	3067.3 (537.2)	2,637 (14.1)	99 (20.9)	251 (23.5)	2,287 (13.3)
	Pakistan	12,656	2945.5 (501.2)	1,316 (10.4)	54 (22.5)	173 (17.3)	1,089 (9.6)
	Angola	9,781	3140.8 (515.0)	1,083 (11.1)	19 (7.4)	24 (8.6)	1,050 (11.2)
	Nigeria	11,048	3126.7 (529.5)	1,247 (11.3)	60 (26.5)	110 (13.7)	1,077 (10.8)
	Nepal	10,474	2888.6 (493.7)	1,874 (17.9)	20 (14.0)	130 (27.5)	1,724 (17.5)
	Uganda	8,522	3227.8 (501.5)	566 (6.6)	23 (23.9)	59 (16.3)	484 (6.0)
	Afghanistan	24,932	3174.7 (455.8)	1,187 (4.8)	35 (14.4)	26 (9.8)	1,126 (4.6)
	DRC	7,631	3013.2 (514.1)	1,037 (13.6)	12 (8.4)	62 (8.9)	963 (14.2)
	Niger	10,737	3098.2 (496.2)	1,679 (15.6)	23 (43.4)	36 (38.7)	1,620 (15.3)
All countries		295,829	3067.3 (527.5)	35,759 (12.1)	915 (21.8)	2,912 (18.6)	31,932 (11.6)

Numbers shown are for singleton births with gestational age 28 to 41 completed weeks.
OPT = Occupied Palestinian Territory; DRC = Democratic Republic of Congo.
doi:10.1371/journal.pone.0105155.t001

Statistical analysis

We divided our sample into two groups by gestational age: preterm (<37 weeks gestational age) and term (37–41 weeks gestational age) deliveries. The characteristics and outcomes of SGA compared to AGA infants in these groups were analysed separately. We compared preterm SGA vs preterm AGA, term SGA vs term AGA.

We performed the Chi-square test by taking into account the clustering and probability-sampling effects of the survey design. Also, after considering the study sampling design and clustering effects (health facility and country) on individual outcomes, we constructed multilevel logistic regression models with random effects for three levels: individual, facility and country. In our analyses of the association between SGA and fresh stillbirths and early neonatal death, we adjusted for maternal age, marital status, education, parity, medical conditions during pregnancy such as chronic hypertension, preeclampsia/eclampsia, severe anaemia, malaria/dengue and HIV/AIDs at the individual level, and capacity of health facilities at the facility level by four categorised HDI groups. The categories comprised as follows: very high HDI countries included Japan, Qatar and Argentina; high HDI countries included Mexico, Lebanon, Peru, Brazil, Ecuador and Sri Lanka; medium HDI countries included Jordan, China, Thailand, Mongolia, the Occupied Palestinian Territory, Paraguay, Philippines, Vietnam, Nicaragua, India and Cambodia, and low HDI countries included Kenya, Pakistan, Angola, Nigeria, Nepal, Uganda, Afghanistan, the Democratic Republic of Congo and Niger. In the 'overall category', we adjusted three-level structure random effects regression models to obtain odds ratios (ORs): individual (level 1), facility (level 2) and country (level 3).

Statistical analysis was conducted using Stata/MP version 12.0 (Stata Corp LP, College Station, Texas) and a P-value<0.05 was considered statistically significant.

Ethics committee approval

The HRP Specialist Panel on Epidemiological Research reviewed and approved the study protocol for technical content. This study was approved by the WHO Ethical Review Committee and the relevant ethical clearance mechanisms in all countries. Written consent from individual participants was not required, although patient records was anonymized and de-identified prior to analysis.

Results

The WHO Multi-country Survey on Maternal and Newborn Health collected a total of 314,623 women's data from 359 health facilities in 29 countries. Excluded from the analysis were deliveries with missing gestational age and birthweight (5,392), pregnancies that lasted less than 28 weeks or more than 42 weeks (6,191); multiple births (4,579), infants with congenital malformation (2,041) and missing infant gender (255). After the exclusions were made, a total of 295,829 deliveries were retained in the analysis. Table 1 presents the mean birthweight and the prevalence of SGA by each country. The overall prevalence of SGA was highest in Cambodia (18.8%), Nepal (17.9%), the Occupied Palestinian Territory (16.1%), and Japan (16.0%), while the lowest was observed in Afghanistan (4.8%), Uganda (6.6%) and Thailand (9.7%). With further exclusion of LGA infants, the sample size was reduced to 245,77, consisting of 210,047 (85.5%) AGA and 35,726 (14.5%) SGA infants, including 3,827 (26.6%) preterm SGA and 31,932 (13.8%) term SGA, respectively. Table 2 indicates rates of SGA by maternal and neonatal characteristics in preterm and term deliveries. The rates of both preterm and term SGA deliveries were consistently high across HDI groups.

Table 3 shows risk factors for SGA in preterm and term deliveries. The risk factors of delivering preterm SGA infants were significantly higher compared to AGA risk factors among nulliparous women (adjusted odds ratio [AOR]: 1.17; 95% CI: 1.06–1.29), and women with chronic hypertension (AOR: 1.68; 95% CI: 1.22–2.30) and preeclampsia/eclampsia (AOR: 2.89; 95% CI: 2.55–3.28). Higher risks of term SGA compared with term AGA were observed among younger (AOR: 1.09; 95% CI: 1.04–1.14) and older women (AOR: 1.07; 95% CI: 1.02–1.13), single women (AOR: 1.11; 95% CI: 1.06–1.17), women with 1–6 years of education (AOR: 1.55; 95% CI: 1.46–1.65), nulliparous women (AOR: 1.45; 95% CI: 1.41–1.50), and women with preeclampsia/eclampsia (AOR: 2.05; 95% CI: 1.88–2.23), anaemia (HB<7 mg/dl) (AOR: 1.30; 95% CI: 1.15–1.47), HIV/AIDS (AOR: 1.48; 95% CI: 1.22–1.80), and other medical conditions (AOR: 1.47; 95% CI: 1.24–1.74). Multiparity (> = 3) (AOR: 0.88; 95% CI: 0.83–0.92) was a protective factor for term SGA and, after adjusting for variables, country HDI had no significant association.

Prevalence of adverse perinatal outcomes for SGA by gestational weeks in each HDI country group is presented in Table 4. We observed a significant trend of higher mortality rates in SGA and all deliveries for lower HDI countries (P<0.001).

The association between SGA deliveries and fresh stillbirths, neonatal near miss, early neonatal deaths, and perinatal deaths compared with AGA deliveries by HDI country group are presented in Table 5 and are stratified by preterm and term delivery. For preterm and term SGA, very high HDI countries had no significant increase in fresh stillbirth, early neonatal mortality and perinatal mortality, although low to high HDI countries had risks two to four times higher than preterm AGA. For neonatal near miss, both preterm and term SGA deliveries had 1.7 to 2.7 times significantly higher risk than AGA, although preterm SGA had a higher prevalence of near miss (50% to 80% among neonates of less than 32 weeks' gestation) than term SGA, irrespective of HDI countries.

Discussion

Main findings

We determined the maternal risk factors and adverse perinatal outcomes in preterm- and term-SGA infants in 29 countries globally using a large multi-country dataset. After adjusting for country-, facility- and individual-level effects, we found no association between increased risks of preterm SGA and socio-demographic status, such as age or education, compared with preterm AGA; however, we did observe that nulliparity and medical conditions, such as chronic hypertension and preeclampsia/eclampsia, were significantly associated with increased risks of preterm SGA compared with preterm AGA.

Strengths and limitations

To the best of our knowledge, this is the most current and extensive multi-country study to compare and examine risk factors and their adverse outcomes in preterm SGA and term SGA deliveries compared with preterm and term AGA deliveries using country-specific generic references. We used SGA criteria that incorporates country-specific reference standards developed by Mikolajczyk et al. [8]. This generic, global reference for fetal-weight and birthweight percentiles is more effective in predicting adverse perinatal outcomes compared with non-customised fetal-weight references, and is easier to use than the customised fetal-

Table 2. Maternal and neonatal characteristics.

	Preterm delivery (≤36 weeks)		p value	Term delivery (≥37 weeks)		p value
	Total deliveries	SGA [n (%)]		Total deliveries	SGA [n (%)]	
All deliveries	14,360	3,827 (26.6)		231,413	31,899(13.8)	
Age						
<20	1,840	530 (28.8)	p<0.05	25,283	4,508 (17.8)	p<0.001
20–34	10,608	2,753 (25.9)		179,550	24,132 (13.4)	
≥35-	1,912	544 (28.4)		26,580	3,292 (12.3)	
Marital status						
Single	1,684	520 (30.8)	p<0.01	24,077	4,122 (17.1)	p<0.001
Married	12,570	3,277 (26.1)		205,625	27,585 (13.4)	
Education, years						
0	1,936	485 (25.0)	0.466	34,276	4,163 (12.1)	p<0.001
1–6	1,948	501 (25.7)		30,242	4,850 (16.0)	
7–9	2,988	776 (25.9)		44,161	6,386 (14.5)	
10–12	4,234	1,176 (27.8)		67,652	9,852 (14.6)	
>12	2,082	584 (28.1)		37,896	4,641 (12.2)	
Parity						
0	6,766	1,889 (27.9)	p<0.05	102,653	16,831 (16.4)	p<0.001
1–2	5,617	1,420 (25.3)		93,762	11,354 (12.1)	
≥3	1,958	511 (26.1)		34,696	3,681 (10.6)	
Mode of delivery						
Vaginal	8,801	2,109 (23.9)	p<0.001	169,114	23,157 (13.7)	0.298
Caesarean	5,538	1,708 (30.8)		62,022	8,709 (14.0)	
Medical conditions						
Chronic hypertension	228	96 (42.1)	p<0.001	703	134 (19.1)	p<0.001
Pre-/eclampsia	1,680	781 (46.5)	p<0.001	4,207	1,031 (24.5)	p<0.001
Anaemia (HB<7 mg/dl)	608	210 (34.5)	p<0.01	2,791	512 (18.3)	p<0.001
Malaria/dengue	55	17 (30.9)	0.540	193	46 (23.8)	p<0.001
HIV/AIDs	99	26 (26.3)	0.935	845	161 (19.1)	p<0.001
Others	318	115 (36.2)	p<0.01	1,221	218 (17.8)	p<0.001
Infant gender						
Male	7,605	1,994 (26.2)	0.248	118,483	15,856 (13.4)	p<0.001
Female	6,755	1,833 (27.1)		112,930	16,043 (14.2)	
Apgar score at 5 minutes <7	1,253	502 (40.1)	p<0.001	4,503	1051 (23.3)	p<0.001
Country HDI						
Very high	768	209 (27.2)	p<0.001	13,725	1,993 (14.5)	p<0.05
High	3,736	1,173 (31.4)		51,470	7,548 (14.7)	
Medium	5,443	1,239 (22.8)		76,203	10,938 (14.4)	
Low	4,13	1,206 (27.3)		90,015	11,420 (12.7)	
Facility capacity						
High	5,053	1,390 (27.5)	0.245	60,857	8,435 (13.8)	0.119
Medium	5,349	1,470 (27.5)		92,575	11,970 (12.9)	
Low	2,552	596 (23.4)		48,288	7,274 (15.1)	

Other medical conditions were included, such as chronic or acute injury or disorders affecting the heart, lungs, liver and kidneys (including pyelonephritis).
Chi-square *p*-values adjusted for survey design.
doi:10.1371/journal.pone.0105155.t002

weight reference. A large sample size and the use of standardized questionnaires across countries allowed us to examine outcomes and stratify countries by five HDI groups.

Our study has several limitations. First, the quality of the data, especially birthweight and gestational age, is questionable in some countries. Errors might occur in dating the pregnancy, especially in countries where gestational age is based on the last menstrual

Table 3. Risk factors for SGA.

	Preterm delivery (≤36 weeks)			Term delivery (≥37 weeks)		
	OR	AOR	95% CI	OR	AOR	95% CI
Age						
<20	1.15*	1.04	(0.89–1.20)	1.39***	1.09	(1.04–1.14)***
20–34	reference					
≥35-	1.13*	1.08	(0.94–1.24)	0.91**	1.07	(1.02–1.13)**
Marital status						
Single	1.27**	1.15	(0.98–1.34)	1.33***	1.11	(1.06–1.17)***
Married	reference					
Education, years						
0	0.85	1.07	(0.88–1.31)	0.99	1.50	(1.41–1.61)***
1–6	0.88	1.03	(0.86–1.23)	1.37***	1.55	(1.46–1.65)***
7–9	0.89	1.01	(0.86–1.19)	1.21***	1.34	(1.27–1.41)***
10–12	0.98	1.02	(0.89–1.18)	1.22***	1.22	(1.17–1.28)***
>12	reference					
Parity						
0	1.14**	1.17	(1.06–1.29)**	1.42***	1.45	(1.41–1.50)***
1–2	reference					
≥3	1.04	0.96	(0.83–1.12)	0.86***	0.88	(0.83–0.92)***
Medical conditions						
Chronic hypertension	2.02***	1.68	(1.22–2.30)**	1.47***	1.20	(0.96–1.49)
Preeclampsia/eclampsia	2.75***	2.89	(2.55–3.28)***	2.06***	2.05	(1.88–2.23)***
Anaemia (HB<7 mg/dl)	1.48***	1.24	(0.99–1.56)	1.41***	1.30	(1.15–1.47)***
Malaria/dengue	1.23	1.16	(0.58–2.32)	1.96***	1.26	(0.83–1.92)
HIV/AIDs	0.98	0.85	(0.50–1.44)	1.47***	1.48	(1.22–1.80)***
Others medical conditions	1.58**	1.24	(0.92–1.67)	1.36**	1.47	(1.24–1.74)***
Country HDI						
Very high	reference					
High	1.22	1.23	(0.64–2.34)	1.01	0.79	(0.39–1.59)
Medium	0.78*	0.88	(0.47–1.63)	0.98	0.85	(0.51–1.44)
Low	1.01	1.28	(0.68–2.42)	0.85*	0.61	(0.37–1.02)

Other medical conditions were included, such as chronic or acute injury or disorders affecting the heart, lungs, liver and kidneys (including pyelonephritis).
SGA = small-for-gestational age; HDI = Human Development Index; OR = odds ratio; AOR = adjusted odds ratio. Three-level structure random effects regression models were used to obtain ORs: individual (level 1), facility (level 2) and country (level 3).
***p<0.001 **p<0.01 *p<0.05.
doi:10.1371/journal.pone.0105155.t003

period or where the birthweight is rounded up or down by a full 100 g. Due to this limitation, we focused on identifying the risk factors of SGA rather than focusing on SGA prevalence in each country.

Another limitation is a lack of data on maternal characteristics that have been noted in previous studies to be associated with the delivery of SGA infants, including smoking, alcohol and caffeine intake, maternal BMI, malnutrition, gestational weight gain, maternal stature, psychosocial stress, interpregnancy interval, and previous history of miscarriage [10–16]. Lack of adjustment for these variables may have led to an overestimation of the risk of SGA delivery, especially for women of a younger or older age, with less education or in low HDI-scoring countries.

Lastly, by using multilevel multiple regression analysis we were able to generalize our findings among facility-based settings; however, adverse perinatal outcomes and maternal medical conditions may have been overestimated because only the most severe cases are presented in higher-level facilities. Furthermore, the risk of neonatal mortality and morbidity could be underestimated due to the 7-day period in this study for neonatal follow-up. It should be noted that mortality due to infections, necrotising enterocolitis and other complications may occur after this period. Thus, the outcomes and conditions cannot be considered representative of the general population.

Interpretation

Our results suggest that nulliparity, chronic hypertension and preeclampsia/eclampsia are associated with a higher risk of preterm SGA. This result is consistent with other studies [18,34]. In a national birth cohort study in Denmark, Catov et al. found that risk of preterm SGA increased 5.5 (95% confidence interval [CI] 3.2–9.4) times and term SGA increased 1.5 (95% CI 1.0–2.2) times among women with chronic hypertension [34]. The result is also consistent with the findings of Villar et al. who analysed data

Table 4. Prevalence of fresh stillbirths and early neonatal mortality by HDI country groups.

Outcome	SGA [n/N (%)]	HDI country group [n/N (%)]				*p*-value
		Very High	High	Medium	Low	
Fresh stillbirth						
All deliveries	2458/244382 (1.0)	31/14426 (0.2)	183/55096 (0.3)	578/81251 (0.7)	1666/93578 (1.8)	p<0.001
SGA deliveries						
≤32	144/797 (18.1)	3/44 (6.8)	20/248(8.1)	41/243 (16.9)	80/262 (30.5)	p<0.001
33–36	169/2748 (6.2)	3/160 (1.9)	27/890 (3.0)	55/920 (6.0)	84/778 (10.8)	p<0.001
≥37	520/31585 (1.7)	3/1987 (0.2)	31/7529 (0.4)	133/10837 (1.2)	353/11232 (3.1)	p<0.001
Neonatal near miss						
All live deliveries	11436/228831 (4.8)	454/14417 (3.2)	3210/54736 (5.9)	4550/80108 (5.7)	3222/91006 (3.5)	p<0.001
SGA deliveries						
≤32	355/484 (73.4)	32/40 (80.0)	160/201 (79.6)	115/145 (79.3)	48/98 (49.0)	p = 0.003
33–36	1011/2419 (41.8)	49/155 (31.6)	396/837 (47.3)	358/801 (44.7)	208/626 (33.2)	p = 0.019
≥37	1889/30785 (6.1)	58/1982 (2.9)	441/7480 (5.9)	826/10603 (7.8)	564/10720 (5.3)	p = 0.016
Early neonatal death						
All live deliveries	1534/241924 (0.6)	19/14426 (0.1)	160/54913 (0.3)	514/80673 (0.6)	841/91912 (0.9)	p<0.001
SGA deliveries						
≤32	162/653 (24.8)	1/41 (2.4)	23/228 (10.1)	56/202 (27.7)	82/182 (45.1)	p<0.001
33–36	152/2579 (5.9)	2/157(1.3)	23/863 (2.7)	61/865 (7.1)	66/694 (9.5)	p<0.001
≥37	267/31065 (0.9)	3/1984 (0.2)	15/7498 (0.2)	93/10704 (0.9)	156/10879 (1.4)	p<0.001
Perinatal death						
All deliveries	3992/244382 (1.6)	50/14457 (0.4)	343/55096 (0.6)	1092/81251 (1.3)	2507/93578 (2.7)	p<0.001
SGA deliveries						
≤32	306/797 (38.4)	4/44 (9.9)	43/248 (17.3)	97/243 (39.9)	162/262 (61.8)	p<0.001
33–36	321/2748 (11.7)	5/160 (3.1)	50/890 (5.6)	116/920 (12.6)	150/778 (19.3)	p<0.001
≥37	787/31585 (2.5)	6/1987 (0.3)	46/7529 (0.6)	226/10837 (2.1)	509/11232 (4.5)	p<0.001

SGA = small-for-gestational age; HDI = Human Development Index Chi-square *p*-values adjusted for survey design.

doi:10.1371/journal.pone.0105155.t004

from WHO antenatal care trials and observed that nulliparity, chronic hypertension and obesity are also risk factors for preeclampsia in developing countries, but not low socioeconomic status [18]. Preeclampsia may cause an inadequate vascular response to abnormal placentation in pregnancy and may represent a distinct pathogenesis, which might affect fetal growth [6,35]. Increased risk screening in antenatal care visits and referral to higher facilities for high-risk cases at an earlier stage in the pregnancy may help to reduce the incidence of severe preeclampsia or eclampsia.

We found that sociodemographic factors such as age, marital status and education were not significantly associated with the risk of preterm SGA, but sociodemographic status factors were related to term SGA. The results indicated that preterm SGA deliveries are more likely to be related to a maternal medical condition, especially preeclampsia, which tends to terminate the pregnancy earlier. On the other hand, term SGA may be more significantly relevant to lifestyle factors, such as sociodemographic status, malnutrition or other factors, and various medical conditions such as anaemia, HIV/AIDS and others. Our results are consistent with other studies that have observed a significant increased risk of term SGA associated with maternal age [10,11] and nulliparity [11,12]. Previous studies confirm that sociodemographic status is associated with a greater risk of SGA, although these studies did not divide SGA by preterm and term delivery [15,36]. Berg et al. conducted path analysis to examine the relationship between maternal education and SGA using population-based cohort study data and showed that a significantly increased risk of SGA delivery among women with less education was related foremost to maternal smoking and, to some degree, to maternal height [15]. A population-based case-control study using Finnish birth register data also confirmed that between high and low socioeconomic status groups, 50% of the difference in risk of SGA was due to smoking [36].

Very high HDI countries showed no significant increase in the mortality risk for preterm and term SGA deliveries. This might be explained by the high quality of intrapartum care including access to care, human resources and drugs or medical equipment in very high HDI countries, which could reduce the mortality risk for preterm and term SGA deliveries. However, low to high HDI countries had risks two to four times higher compared to preterm AGA. These results are consistent with the population-based secondary analysis conducted in 20 cohorts in LMICs by the Child Health Epidemiology Reference Group (CHERG), which showed that the risk of early neonatal mortality increased about 16 times for preterm SGA delivery compared with preterm non-SGA delivery [37]. The reason for these different degrees of mortality risk might be due to the definition of SGA used by the authors, which they adapted from the US population birthweight reference standard and applied to LMICs. Another population-based cohort study in France showed that the risk of stillbirth was 2.6 times higher in preterm SGA deliveries, which is a similar result to our

Table 5. The association between SGA and perinatal outcomes compared with AGA by HDI country groups.

HDI group	Preterm delivery (≤36 weeks)		Term delivery (≥37 weeks)		All deliveries	
	AOR	95% CI	AOR	95% CI	AOR	95% CI
Fresh stillbirth						
Very high	0.31	(0.06–1.76)	1.79	(0.29–10.9)	1.46	(0.47–4.51
High	2.31	(1.36–3.93)**	3.00	(1.75–5.12)***	3.70	(2.56–5.33)***
Medium	2.18	(1.62–2.96)***	3.08	(2.43–3.89)***	2.97	(2.47–3.56)***
Low	1.99	(1.54–2.57)***	2.89	(2.47–3.37)***	3.07	(2.69–3.51)***
Overall[§]	2.01	(1.66–2.42)***	2.95	(2.60–3.36)***	3.07	(2.77–3.41)***
Neonatal near miss						
Very high	2.34	(1.47–3.71)***	1.65	(1.13–2.42)**	2.61	(2.02–3.37)***
High	2.60	(2.17–3.11)***	1.69	(1.48–1.93)***	2.47	(2.24–2.71)***
Medium	2.32	(1.98–2.74)***	2.38	(2.17–2.61)***	2.43	(2.26–2.63)***
Low	2.43	(1.97–2.99)***	1.75	(1.57–1.95)***	2.03	(1.85–2.23)***
Overall[§]	2.65	(2.37–2.96)***	1.99	(1.87–2.12)**	2.39	(2.27–2.51)***
Early neonatal death						
Very high	1.19	(0.25–5.74)	1.39	(0.15–12.32)	2.14	(0.67–6.94)
High	3.77	(1.97–6.47)***	2.14	(1.09–4.20)*	3.92	(2.57–5.97)***
Medium	2.77	(2.08–3.68)***	3.44	(2.61–4.56)***	3.56	(2.93–4.32)***
Low	2.92	(2.21–3.83)***	2.94	(2.37–3.63)***	3.53	(3.00–4.16)***
Overall[§]	2.86	(2.36–3.46)***	3.01	(2.56–3.56)***	3.52	(3.12–3.96)***
Perinatal death						
Very high	0.69	(0.22–2.16)	1.78	(0.46–6.82)	1.76	(0.78–3.99)
High	2.89	(1.94–4.31)***	2.63	(1.73–3.99)***	3.80	(2.88–5.02)***
Medium	2.61	(2.10–3.25)***	3.27	(2.72–3.92)***	3.29	(2.88–7.77)***
Low	2.51	(2.06–3.06)***	2.92	(2.58–3.32)***	3.31	(2.98–3.67)***
Overall[§]	2.50	(2.17–2.87)***	3.00	(2.71–3.32)***	3.31	(3.06–3.59)***

The reference category is infants with a birthweight that is appropriate for gestational age in each subgroup analysis.
SGA = small-for-gestational age; AGA = appropriate-for-gestational age; HDI = Human Development Index, AOR = adjusted odds ratio.
Two-level structure random effects regression models were used to obtain ORs: individual (level 1) and facility (level 2). Adjusted for maternal age, marital status, education, parity, medical conditions during pregnancy such as chronic hypertension, preeclampsia/eclampsia, severe anaemia, malaria/dengue, HIV/AIDs at the individual level, and capacity of health facilities at the facility level.
[§]Three-level structure random effects regression models were used to obtain ORs: individual (level 1), facility (level 2) and country (level 3). Same adjustment at individual and facility level and additional adjustment for country HDI at the country level.
***p<0.001 **p<0.01 *p<0.05.

doi:10.1371/journal.pone.0105155.t005

overall mortality risks [38]. Simchen et al. found that singleton preterm SGA infants had a significantly higher mortality rate with more culture-proven sepsis episodes [23].

In our findings, the risk of mortality in both preterm and term SGA deliveries was higher compared to preterm and term AGA, respectively, in low to high HDI countries. However, very high HDI countries had no significant mortality difference between preterm SGA and AGA, but had higher risks of mortality for term SGA, especially in fresh stillbirths.

Our findings indicate that if LMICs give appropriate care comparable with very high HDI countries, such as including regular risk screening in antenatal care visits and providing adequate treatment and care to those who need treatment at an earlier stage, it might be possible to decrease perinatal mortality among preterm SGA infants. Term SGA infants were three to four times significantly more likely to experience perinatal mortality than term AGA infants, irrespective of HDI groups. This finding supports Lubchenco's report from 1976, which found that the risk of neonatal mortality was six times more likely in term SGA infants compared with term AGA infants [39]. Risk of perinatal mortality is significantly higher among term SGA deliveries compared with preterm AGA deliveries, irrespective of quality of care.

Neonatal near miss is higher risk, irrespective of HDI, although it has a high prevalence in neonates born at less than 32 weeks' gestation. In very high HDI countries, 80% of neonates born at less than 32 gestational weeks experienced neonatal near miss, although perinatal mortality was around 11%. In low HDI countries, 49% of neonates born at less than 32 gestational weeks experienced neonatal near miss, and 70% of them died. The quality of neonatal intensive care is vital to prevent mortality.

Neonatal clinical management should be considered in the development of health policies for reducing neonatal mortality, such as screening high-risk neonates for early complications and the referral of pregnant women with hypertensive diseases for delivery in health facilities with special care units. Careful follow-up is necessary for SGA neonates who are at a higher risk of acquiring non-communicable diseases in the future.

Further research could define SGA using the customized rather than standard intrauterine growth curves, especially for countries that adopt curves based on populations from diverse ethnic

groups. Ideally the standard questionnaire should include variables such as weight gain during pregnancy and pre-pregnancy BMI.

Conclusion

Our results demonstrate that preterm SGA is associated with medical conditions related to chronic hypertension and pre-eclampsia/eclampsia, but is not associated with sociodemographic status. This result clearly identified that global prevention for preterm SGA should mainly focus on preeclampsia. Term SGA is associated with sociodemographic status and various medical conditions. Risk of fresh stillbirth and neonatal death was two to three times higher in preterm SGA in LMICs, except in the very high HDI group. Term SGA was significantly associated with perinatal deaths irrespective of HDI categories.

Acknowledgments

The Multi-country Survey on Maternal and Newborn Health is a research project implemented by the WHO in a global network of health facilities between 2010 and 2011. This project is part of the WHO response to the United Nations Secretary-General call for action for improving women's and children's health around the world. In this connection, the Organization is grateful to the extensive network of institutions and individuals who contributed to the project design and implementation, including researchers, study coordinators, data collectors, data clerks and other partners including the staff from the Ministries of Health and WHO offices.

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Further information on the Multi-country Survey on Maternal and Newborn Health and derivatives can be found at: http://www.who.int/reproductivehealth/topics/maternal_perinatal/nearmiss

Author Contributions

Conceived and designed the experiments: EO TG. Performed the experiments: JPS RM. Analyzed the data: TG EO. Contributed reagents/materials/analysis tools: EO. Wrote the paper: EO. Contributed to the interpretation of the analysis and reviewed the manuscript: NM JPV CP EOP. Reviewed and approved final version of the manuscript: EO TG NM JPV CP EO JPS RM.

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DOI: 10.1111/1471-0528.12647
www.bjog.org

Original article

Indirect causes of severe adverse maternal outcomes: a secondary analysis of the WHO Multicountry Survey on Maternal and Newborn Health

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Accepted 16 January 2014.

Objective To assess the proportion of severe maternal outcomes resulting from indirect causes, and to determine pregnancy outcomes of women with indirect causes.

Design Secondary analysis of the WHO Multicountry Survey on Maternal and Newborn Health.

Setting A total of 359 health facilities in 29 countries in Africa, Asia, Latin America, and the Middle East.

Sample A total of 314 623 pregnant women admitted to the participating facilities.

Methods We identified the percentage of women with severe maternal outcomes arising from indirect causes. We evaluated the risk of severe maternal and perinatal outcomes in women with, versus without, underlying indirect causes, using adjusted odds ratios and 95% confidence intervals, by a multilevel, multivariate logistic regression model, accounting for clustering effects within countries and health facilities.

Main outcome measures Severe maternal outcomes and preterm birth, fetal mortality, early neonatal mortality, perinatal mortality, low birthweight, and neonatal intensive care unit admission.

Results Amongst 314 623 included women, 2822 were reported to suffer from severe maternal outcomes, out of which 20.9% (589/2822; 95% CI 20.1–21.6%) were associated with indirect causes. The most common indirect cause was anaemia (50%). Women with underlying indirect causes showed significantly higher risk of obstetric complications (adjusted odds ratio, aOR, 7.0; 95% CI 6.6–7.4), severe maternal outcomes (aOR 27.9; 95% CI 24.7–31.6), and perinatal mortality (aOR 3.8; 95% CI 3.5–4.1).

Conclusions Indirect causes were responsible for about one-fifth of severe maternal outcomes. Women with underlying indirect causes had significantly increased risks of severe maternal and perinatal outcomes.

Keywords Indirect causes, maternal mortality, maternal near miss, perinatal outcomes, severe maternal outcomes.

Please cite this paper as: Lumbiganon P, Laopaiboon M, Intarut N, Vogel JP, Souza JP, Gülmezoglu AM, Mori R, on behalf of the WHO Multicountry Survey on Maternal and Newborn Health Research Network. Indirect causes of severe adverse maternal outcomes: a secondary analysis of the WHO Multicountry Survey on Maternal and Newborn Health. BJOG 2014; 121 (Suppl. 1): 32–39.

Introduction

Maternal death is defined as the death of a woman while pregnant or within 42 days of a termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes (International Statistical Classification of Diseases and Related Health Problems, 10th edition, ICD–10). Causes of maternal death are classified as direct, indirect, and incidental. Direct maternal death is the result of complications or management of the pregnancy and delivery: e.g.

pre-eclampsia/eclampsia, haemorrhage, puerperal sepsis, etc. Indirect maternal mortality is defined as a pregnancy-related death in a mother with a pre-existing or newly developed health problem unrelated to pregnancy, such as cardiac disease, HIV/AIDS, or chronic hypertension. Incidental or non-obstetrical maternal deaths are deaths unrelated to pregnancy, such as death in a car crash. Millennium Development Goal (MDG) 5 aimed at a 75% reduction in maternal mortality ratio (MMR) from 1990 to 2015; however, only 23 out of 180 countries are on track to achieve this goal.[1]

Recent reports indicated that indirect causes were responsible for about a quarter of all maternal deaths.[2,3] The main indirect causes included anaemia, cardiac disease, HIV/AIDS, and cerebrovascular disease.[4–9] In 2009, WHO, through an international consultative process, developed a standard definition of maternal near miss, using markers of organ dysfunction during pregnancy, childbirth, or after birth.[10] Thus, a severe maternal outcome (SMO), including both maternal deaths and near-miss cases, is a more robust indicator for evaluating the quality of maternal health care.[10] The main findings of the WHO Multicountry Survey (WHOMCS), which aimed to assess the burden of complications related to pregnancy and the coverage of key maternal health interventions, was published recently.[11] This secondary analysis provides an opportunity for an in-depth exploration of indirect causes associated with severe adverse outcomes for mothers and their newborns. This analysis will also provide collective data from a large number of countries involving an extremely high number of women. The objectives of this secondary analysis of the WHOMCS were to evaluate, in depth, the indirect causes of women with SMO, and to assess maternal and perinatal outcomes of women with pre-existing or newly developed health problems unrelated to pregnancy (underlying indirect causes).

Methods

Study design and setting

The design of the WHOMCS is described in detail elsewhere.[11,12] In brief, this is a multicentre, cross-sectional study aimed to study the occurrence of severe maternal morbidity in a worldwide network of health facilities. It was approved by the World Health Organization Ethical Review Committee and implemented in a random sample of 359 health facilities in 29 countries from Africa, Asia, Latin America, and the Middle East. Because of the financial and practical constraints, we did not conduct the survey in developed countries except for Japan, which volunteered to participate. A stratified, multistage cluster sampling strategy was used to select countries, provinces, and health facilities. Within each country, the capital city was sampled, along with two randomly selected provinces (probability proportional to population). From these, seven facilities with over 1000 deliveries per year and the capacity to perform caesarean sections were randomly selected.

The study population included women giving birth, from which data on all maternal near-miss and maternal death cases, regardless of the gestational age and delivery status, and all maternal deaths during the study period between 1 May 2010 and 31 December 2011 were collected.

Data collection took place on two levels: individual and facility levels. At the individual level, data related to pregnancy outcomes, severe complications, and the management of women in the study, and their respective newborns, were extracted from medical records of the participating facilities by trained research assistants. At the facility level, data on characteristics of each health facility, and their ability to identify and manage severe complications, were collected through a specific survey using a pre-tested questionnaire among the professionals responsible for the participating facilities. This was to be used in the adjustment for the evaluation of the association between indirect maternal causes and pregnancy outcomes. The period of data collection ranged from 2 to 4 months, depending on the annual number of deliveries at the participating facilities.

Variables and definitions

We defined indirect causes as conditions resulting from pre-existing or newly developed disease during pregnancy, and not caused by direct obstetric conditions. From the multicountry survey database, this included: (1) infections (other than HIV, AIDS, HIV wasting syndrome, and malaria/dangue), including pyelonephritis, influenza-like illness, sepsis, and other systemic infections; (2) hypertensive disorders (chronic hypertension, defined as blood pressure >140/90 mmHg before 20 weeks of gestation); and (3) other complications or diseases, including HIV, AIDS, HIV wasting syndrome, severe anaemia (defined as haemoglobin <7 g%), malaria/dengue, cancer, heart disease, lung disease, renal disease, and hepatic disease.

For maternal outcomes, we studied maternal near miss (MNM), maternal death (MD), and severe maternal outcome (SMO). We defined MNM as a woman who nearly died but survived a complication that occurred during pregnancy, childbirth, or within 7 days of a termination of pregnancy. MD was defined as the death of a woman while pregnant or within 7 days of a termination of pregnancy. SMO was defined as a woman having had a MD or MNM up to 7 days after giving birth or after a termination of pregnancy, irrespective of gestational age or delivery status.[11]

For adverse perinatal outcomes, we studied preterm birth, fetal mortality, early neonatal mortality, perinatal mortality, neonatal intensive care unit (NICU) admission, and an Apgar score <7 at 5 minutes. We defined preterm birth as any birth before 37 weeks of gestation. Fetal mortality was defined as any death of a fetus after 20 weeks of

gestation or with a fetal weight of 500 g. Early neonatal mortality was defined as the death of a liveborn infant within the first 7 days of life.

Potential confounding factors were assessed for both facility and individual characteristics. Potential confounding factors for the facility included the availability of a blood bank, an adult intensive care unit for adverse maternal outcomes, and an NICU for adverse perinatal outcomes. Potential confounding factors for individuals included maternal demographic and labour characteristics (i.e. marital status, maternal education/years of school attendance as proxies for socio-economic status) and parity. Labour characteristics included onset of labour, fetal presentation, and mode of delivery. Countries were stratified by MMR,[11] and this was counted as a confounding factor at the country level.

Statistical analysis

Frequencies and 95% confidence intervals (95% CIs) were used to describe the underlying indirect causes of women with SMO, MNM, and MD. Frequencies were also used to present the prevalence of obstetric complications, maternal adverse outcomes, and perinatal adverse outcomes among women with and without underlying indirect causes.

The association between the underlying indirect causes and (1) obstetric complications, (2) maternal adverse outcomes, and (3) perinatal adverse outcomes were analysed using a multilevel, multivariate logistic regression model by the procedure GLIMMIX in SAS 9.1. This procedure was intended to account for clustering effects within countries and health facilities. The analysis was also adjusted for the potential confounding factors, including maternal and health facility characteristics and country groups. For this analysis, maternal school attendance was classified according to the UNESCO international standard classification of education. This classification allocates individuals to one of five categories, which correspond to the level of education expected after a given number of years of education: no education (zero years); primary (1–6 years); lower secondary (7–9 years); upper secondary (10–12 years); post-secondary/tertiary (>12 years).

The combination of underlying indirect causes and obstetric complications was performed to consider the trend of increased risks for individual adverse outcomes. Our main interest was to assess the risks among women with underlying indirect causes and (1) with obstetric complications (called combination causes), and (2) without obstetric complications. The association analysis for perinatal adverse outcomes was performed in a sample of singleton pregnant women because the effect of underlying indirect cause in women with multiple births might be biased as a result of the multiple births.

Risks of individual outcomes associated with underlying indirect causes were presented by adjusted odds ratios (aORs), with corresponding 95% confidence intervals (95% CIs). Statistical analysis was performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Prevalence of indirect causes among women with SMO

Amongst the 314 623 women included in the WHOMCS there were 3024 women with SMO (Figure 1). Missing data for some complications was observed in 202 women with SMO. Therefore, 2822 (93.3%) women with SMO were available in this analysis: 2365 women with MNM and 457 MDs.

The prevalence of underlying indirect causes in women with SMO was 20.9% (589/2822; 95% CI 20.1–21.6%). They were classified into 19.8% (467/2365) among women with MNM, and 26.7% (122/457) among MDs. Details of individual underlying indirect causes among women with SMO, MNM, and MD are shown in Table 1. Some women could have more than one cause. The prevalence of the underlying indirect causes resulting from other conditions or diseases, such as anaemia, malaria, HIV, AIDS, HIV wasting syndrome, etc., were very high in the women with SMO (82.5%), MNM (81.6%), and MD (86.1%). The most common single cause was anaemia, which was found in about 50% of women with SMO. The other causes varied from only 1.0% with cancer to 16.6% with malaria/dengue among women with SMO. The prevalences of hepatic disease and of HIV, AIDS, HIV wasting syndrome were 11.5% for each in MD, and very much higher than those of women with MNM: 7.5 and 1.9%, respectively.

For underlying indirect causes resulting from infections, the prevalence of each infection varied greatly between women with MNM and MD. The common infections were sepsis and other systemic infections: 15.2% among women with MNM, and very high, up to 41.0%, in MDs. Pyelonephritis and influenza-like illness were more frequent among women with MNM (10.5 and 4.5%, respectively), than among MDs (3.3 and 1.6%, respectively). Chronic hypertension was also more frequent among women with MNM, 8.1%, than in MDs, 4.1%.

Association of underlying indirect causes and maternal adverse outcomes

After excluding 49 women with missing complication conditions, overall 314 574 women were used in the analysis for this association. They were classified into women with underlying indirect causes for 3.5% (11 163 women) and women without underlying indirect causes for 96.5% (303 411 women). The prevalence of obstetric complications was very much higher among women with underlying indirect causes, 31.1%, with a significant aOR of 7.0 (95% CI 6.6–7.4), compared with 3.8% among women without underlying indirect causes (Figure 2; Table 2).

Figure 2 and Table 3 show significant associations between underlying indirect causes and prevalence of SMO, MNM, and MD. The women with underlying indirect causes had a significantly increased risk of SMO, 14.3% (aOR 27.9; 95% CI 24.7–31.6), when compared with only 0.39% among women without underlying indirect causes. Significant trends of increased risk of SMO were observed among women with underlying indirect causes and without obstetric complications (7.7%; aOR 10.7; 95% CI 9.1–12.7), and among women with combination causes (28.9%; aOR 73.0; 95% CI 63.2–84.2), when compared with risks among women without underlying indirect causes. Similar patterns of associations were also observed for the prevalence of MNM and MD (details shown in Table 3).

Association of underlying indirect causes and perinatal adverse outcomes

The prevalence of all perinatal adverse outcomes, such as preterm birth, stillbirth, etc., for each category of underlying indirect causes is presented in Figure 3. An increasing prevalence of individual outcomes was observed among women without and with a combination of underlying indirect causes and obstetric complications. For example,

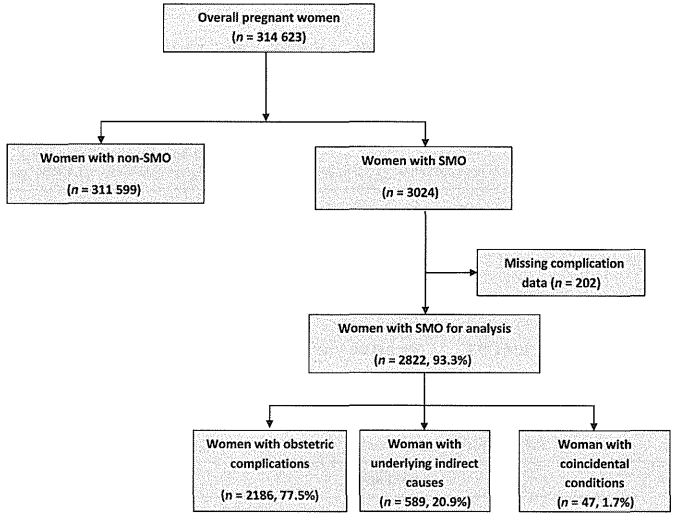

Figure 1. Prevalence of underlying indirect causes in women with severe maternal outcomes.

Table 1. Prevalence of underlying indirect causes among maternal severe outcomes

Causes	SMO *n* (%)	MNM *n* (%)	MD *n* (%)
Overall	2822	2365	457
Indirect causes; *n* (%; 95% CI)	589 (20.9; 20.1–21.6)	467 (19.8; 18.9–20.6)	122 (26.7; 24.6–28.8)
Other complications or diseases	486 (82.5)	381 (81.6)	105 (86.1)
Anaemia	295 (50.1)	234 (50.1)	61 (50.0)
Malaria/dengue	98 (16.6)	79 (16.9)	19 (15.6)
Lung disease	64 (10.9)	47 (10.1)	17 (13.9)
Heart disease	50 (8.5)	38 (8.1)	12 (9.8)
Hepatic disease	49 (8.3)	35 (7.5)	14 (11.5)
HIV, AIDS, and HIV wasting syndrome	23 (3.9)	9 (1.9)	14 (11.5)
Renal disease	20 (3.4)	16 (3.4)	4 (3.3)
Cancer	6 (1.0)	3 (0.6)	3 (2.5)
Infection	184 (31.2)	133 (28.5)	51 (41.8)
Sepsis and other systemic infections	121 (20.5)	71 (15.2)	50 (41.0)
Pyelonephritis	53 (9.0)	49 (10.5)	4 (3.3)
Influenza-like illness	23 (3.9)	21 (4.5)	2 (1.6)
Hypertensive disorders			
Chronic hypertension	43 (7.3)	38 (8.1)	5 (4.1)

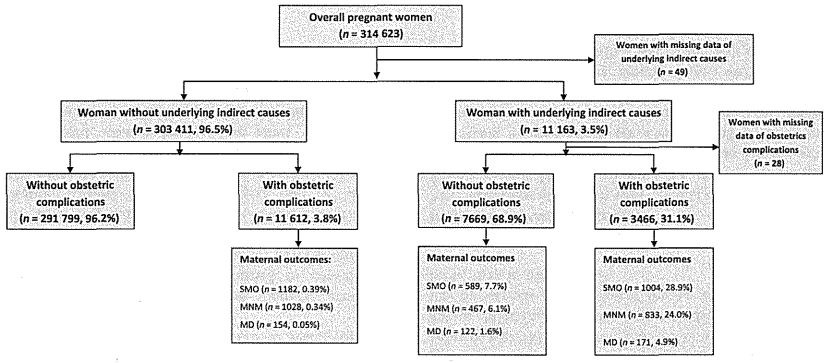

Figure 2. Flow of data for maternal adverse outcomes in women with and without underlying indirect causes.

Table 2. Comparison of obstetric complications of women with and without underlying indirect causes

	Women	Obstetric complications *n* (%)	aOR* (95% CI)
Without underlying indirect causes	303 411	11 612 (3.8)	1
With underlying indirect causes	11 135	3466 (31.1)	7.0 (6.6–7.4)

*Adjusted for levels of MMR, blood bank, adult intensive care unit, marital status, maternal school attendance, parity, onset of labour, fetal presentation, and mode of delivery.

Table 3. Association between underlying indirect causes and maternal adverse outcomes

	aOR* (95% CI)		
	SMO	MNM	MD
Without underlying indirect causes	1	1	1
With underlying indirect causes	**27.9 (24.7–31.6)**	**25.0 (21.8–28.6)**	**36.6 (27.2–49.1)**
Underlying indirect causes and without obstetric complications	10.7 (9.1–12.7)	9.2 (7.6–11.1)	19.5 (13.5–28.1)
Combination causes	73.0 (63.2–84.2)	63.8 (54.7–74.4)	80.0 (57.5–111.3)

Bold values indicates the overall risk of women with underlying indirect causes.
*Adjusted for levels of MMR, blood bank, adult intensive care unit, marital status, maternal education, parity, onset of labour, fetal presentation, and mode of delivery.

the prevalence of stillbirths was 1.6, 7.9, 5.7, and 15.8% for women without underlying indirect causes, women with underlying indirect causes, women with underlying indirect causes without obstetric complications, and women with underlying indirect causes with obstetric complications, respectively.

The aORs of individual perinatal adverse outcomes significantly increased according to the combination of underlying direct causes and obstetric complications. There were significant trends of increased risk of all perinatal adverse outcomes according to the combination causes. Details of the aORs and their 95% CIs are presented in Table 4. For example, the aOR for preterm birth was 2.8 (95% CI 2.7–3.0) among women with underlying indirect causes, when compared with women without underlying indirect causes. Furthermore, the aORs were shown as 2.2 (95% CI 2.1–2.4) among women with underlying indirect causes and without obstetric complications, and up to 4.9 (95% CI 4.5–5.5) among women with combination causes, when compared with women without underlying indirect causes.

Discussion

Main findings

In this population, the prevalence of SMO was 0.96% (0.81% MNM and 0.15% MD). Among women with

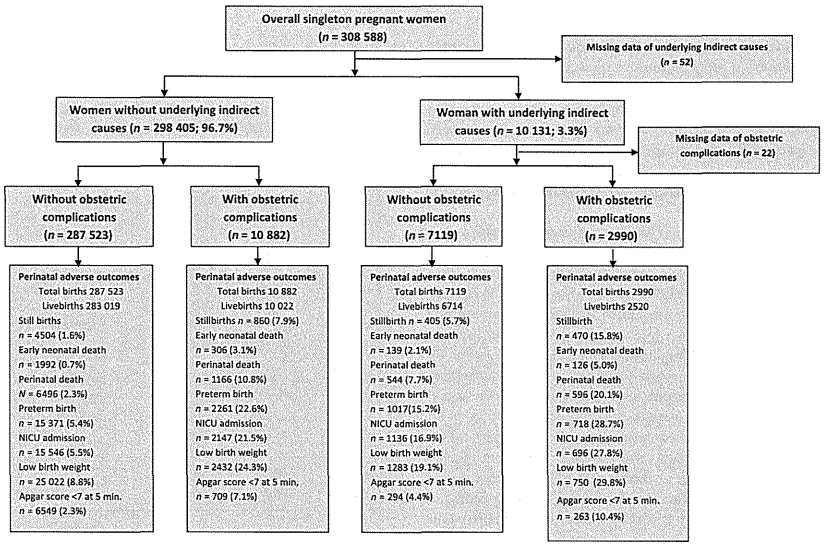

Figure 3. Flow of data for perinatal adverse outcomes in women with and without underlying indirect causes.

Table 4. Association between underlying indirect causes and perinatal adverse outcomes

	aOR (95% CI)*						
	Preterm birth (<37 weeks)	Stillbirth	Early neonatal mortality	Perinatal mortality	Low- birthweight (<2500 g)	NICU admission**	Apgar score <7 at 5 minutes
Without underlying indirect causes	1	1	1	1	1	1	1
With underlying indirect causes	**2.8 (2.7–3.0)**	**4.3 (3.9–4.7)**	**2.6 (2.3–3.0)**	**3.8 (3.5–4.1)**	**2.5 (2.4–2.7)**	**2.8 (2.6–3.0)**	**1.9 (1.7–2.1)**
With underlying indirect causes and without obstetric complications	2.2 (2.1–2.4)	3.0 (2.7–3.4)	1.9 (1.6–2.3)	2.6 (2.3–2.9)	2.0 (1.9–2.2)	2.3 (2.1–2.4)	1.5 (1.3–1.7)
Combination causes	4.9 (4.5–5.5)	9.1 (7.9–10.3)	5.0 (4.0–6.1)	8.0 (7.1–8.9)	4.4 (4.0–4.9)	4.4 (4.0–4.9)	2.9 (2.5–3.4)

*All models were adjusted for levels of MMR, blood bank, neonatal intensive care unit, marital status, maternal school attendance, parity, onset of labour, fetal presentation, and mode of delivery.
**Adjusted for levels of MMR, marital status, maternal school attendance, parity, onset of labour, fetal presentation, and mode of delivery.

SMO, 20.9% were associated with indirect causes. For MD, 26.7% were associated with indirect causes. The main indirect causes included anaemia (50%), malaria/dengue (17%), lung disease (11%), heart disease (9%), and hepatic disease (8%). Women with underlying indirect causes had a seven-fold increased risk of obstetric

complications, 28–fold increased risk of SMO, four-fold increased risk of perinatal mortality, and three-fold increased risk of preterm birth.

Strengths and limitations

This is a large, multicountry study that used pretested, standardised data collection forms by trained data collectors in institutes with experience from the previous WHO Global Survey;[13] however, the cross-sectional data collection might have some limitation on the temporal sequence between underlying indirect causes and obstetric complications. Also, our analysis did not have information on some potential confounding factors known to be associated with SMO and perinatal morbidity and mortality, such as smoking, obesity, diabetes, syphilis, prolonged labour, and some socio-economic factors. As we used medical records as our primary data source, missing data or errors in these records could have affected the data quality; however, we have tried our best to minimise this by using pretested, standardised data collection forms and by intensively training our data collectors before the study.

Interpretation (findings in light of other evidence)

We performed an extensive literature search, but could not find any report evaluating the causes of SMO, so cannot directly compare the proportion of indirect causes of SMO with other reports. We are therefore comparing against other reports that describe the proportion of indirect causes on MD. A very recent report from India including 39 704 live births and 120 MDs showed that 27.5% of MDs were the result of indirect causes, with anaemia and jaundice being the two most common causes.[2] The maternal death surveillance system (MDSS) in Morocco, including 313 reviewed records, found that 13.5% were classified as indirect cause, and that heart disease was the main indirect cause of death.[14] A hospital-based review of maternal mortality in Ghana of 30 269 live births and 322 MDs indicated that 22.4% were from indirect causes, and that infection and sickle cell disease accounted for 61.1% of indirect causes.[3] A systematic review of 12 articles from developed countries between 1980 and 2007 with 9750 MDs showed that 28.6% were from indirect causes, with cardiovascular disease as the main cause.[6] A community-based study from Sudan using a reproductive age mortality survey (RAMOS) showed that 29.7% of MDs were from indirect causes, with severe anaemia and acute febrile illness as the two leading causes.[15] From these previous studies, indirect causes were responsible for 13.5–29.7% of MDs, whereas indirect causes were responsible for 20.9% for SMO in our current analysis.

Anaemia was the most common indirect cause of SMO in this current analysis. This is in accordance with other reports from developing countries;[3,4,15] however, cardiac disease was the leading indirect cause of MD from developed countries.[5–8,14,16]

HIV/AIDS is an increasing contributor of indirect as well as direct causes of MDs in many countries, especially in sub-Saharan Africa.[9,17–19] The most common causes of MD among women with HIV were AIDS, pneumonia, tuberculosis, and meningitis.[20] The prevalence of HIV/AIDS in this current report was very low, and should be cautiously interpreted because of the high possibility of under-reporting.

This analysis indicated very clearly that women with underlying indirect causes had a significantly increased risk of obstetric complications, MNM, and MD, as well as perinatal outcomes. These indirect causes contributed to about a quarter of all women with severe maternal outcomes. In order to improve maternal health globally, healthcare providers should also be aware of the effects of these underlying maternal conditions. These conditions, especially anaemia and cardiac disease, should be detected and corrected before women become pregnant. During pregnancy, special care for women with underlying conditions should be provided, as appropriate.

Conclusion

Indirect causes were responsible for about 21 and 27% of SMOs and MDs, respectively. The main indirect causes included anaemia, malaria/dengue, lung disease, heart disease, and hepatic disease. Women with underlying indirect causes had a significantly increased risk of obstetric complications, SMO, perinatal morbidity, and mortality. To improve maternal health globally, maternal health policies at all levels should also focus on appropriate and timely interventions to reduce the impact of indirect causes of SMO and MD. More research should be conducted to reduce the impact of common indirect causes on SMO.

Disclosure of interests

We declare that we have no conflicts of interest.

Contribution to authorship

PL, ML, JV, JPS, RM, and MG conceptualised the research question. PL and ML drafted the analysis plan. ML and NI analysed the data. PL and ML drafted the article. All authors reviewed and approved the final version of the article.

Details of ethics approval

The HRP Specialist Panel on Epidemiological Research reviewed and approved the study protocol for technical content. This study was approved by the World Health Organization Ethical Review Committee and the relevant ethical clearance mechanisms in all countries (protocol ID A65661; 27 October 2009).

Funding

This study was financially supported by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP); World Health Organization (WHO); United States Agency for International Development (USAID); Ministry of Health, Labour and Welfare of Japan; and Gynuity Health Projects. The sponsors had no role in data collection, analysis, or interpretation of the data, the writing of the report, or the decision to submit for publication. All authors had access to the analysis plan, the outputs of that analysis, and could see the data if they wished to do so. All authors participated in the final discussion and approved the submission.

Acknowledgements

The authors wish to thank all members of the WHO Multicountry Survey on Maternal and Newborn Health Research Network, including regional and country coordinators, data collection coordinators, facility coordinators, data collectors, and all staff at the participating facilities who made the survey possible. We also thank Annette Peters for her kind assistance in copy-editing. Further information on the Multicountry Survey on Maternal and Newborn Health and derivatives can be found at http://www.who.int/reproductivehealth/topics/maternal_perinatal/nearmiss/en/. ■

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DOI: 10.1111/1471-0528.12632
www.bjog.org

Original article

Maternal and institutional characteristics associated with the administration of prophylactic antibiotics for caesarean section: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health

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Accepted 4 November 2013.

Objective To illustrate the variability in the use of antibiotic prophylaxis for caesarean section, and its effect on the prevention of postoperative infections.

Design Secondary analysis of a cross-sectional study.

Setting Twenty-nine countries participating in the World Health Organization Multicountry Survey on Maternal and Newborn Health.

Population Three hundred and fifty-nine health facilities with the capacity to perform caesarean section.

Methods Descriptive analysis and effect estimates using multilevel logistic regression.

Main outcome measures Coverage of antibiotic prophylaxis for caesarean section.

Results A total of 89 121 caesarean sections were performed in 332 of the 359 facilities included in the survey; 87% under prophylactic antibiotic coverage. Thirty five facilities provided 0–49% coverage and 77 facilities provided 50-89% coverage. Institutional coverage of prophylactic antibiotics varied greatly within most countries, and was related to guideline use and the practice of clinical audits, but not to the size, location of the institution or development index of the country. Mothers with complications, such as HIV infection, anaemia, or pre-eclampsia/eclampsia, were more likely to receive antibiotic prophylaxis. At the same time, mothers undergoing caesarean birth prior to labour and those with indication for scheduled deliveries were also more likely to receive antibiotic prophylaxis, despite their lower risk of infection, compared with mothers undergoing emergency caesarean section.

Conclusions Coverage of antibiotic prophylaxis for caesarean birth may be related to the perception of the importance of guidelines and clinical audits in the facility. There may also be a tendency to use antibiotics when caesarean section has been scheduled and antibiotic prophylaxis is already included in the routine clinical protocol. This study may act as a signal to re-evaluate institutional practices as a way to identify areas where improvement is possible.

Keywords Caesarean section, guidelines, health inequity, infection, antibiotic prophylaxis, risk factors.

Please cite this paper as: Morisaki N, Ganchimeg T, Ota E, Vogel JP, Souza JP, Mori R, Gülmezoglu AM, on behalf of the WHO Multicountry Survey on Maternal and Newborn Health Research Network. Maternal and institutional characteristics associated with the administration of prophylactic antibiotics for caesarean section: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG 2014; 121 (Suppl. 1): 66–75.

Introduction

Caesarean section is the most important factor known to be associated with postpartum bacterial infections, with a rate of infection reported to be 1–25%,[1–4] which is 5–20 times higher than that of vaginal delivery.[5,6] There is clear evidence that prophylactic antibiotics for caesarean section reduce the risk of endometritis and other bacterial infections,[7,8] even in low-risk (before labour and with intact membranes) pregnancies,[7,9] and the use of universal prophylactic antibiotics has been widely accepted in guidelines for many countries, including the USA[6,10,11] and several Asian countries.[12] However, reports showed that there are barriers to changing practices (to provide prophylaxis for all caesarean births),[8,13–15] with ongoing debate about whether it is possible to identify certain high- or low-risk groups in order to tailor prophylaxis.[6,13,15–18]

In a previous study of facility deliveries in 29 countries, we reported that the caesarean section rate was 28.6% and that 13% of these were not administered prophylactic antibiotics.[19] In this secondary analysis, we describe the maternal and institutional characteristics associated with a lack of provision of prophylactic antibiotics for caesarean section, and whether clinical relevance alone is enough to adjust our practices.

Methods

Study population

This is a secondary data analysis of the WHO Multicountry Survey on Maternal and Newborn Health, a cross-sectional survey that was conducted in 359 health facilities in 29 countries in Africa, Asia, Latin America and the Middle East.[19,20] In brief, a multi-stage cluster sampling method was used to obtain a sample of health facilities in two randomly selected provinces and the capital city of each country. All women who were admitted for delivery or who had severe maternal outcomes during the study period were included in the study. Trained medical staff retrieved demographics and reproductive characteristics, medical conditions during pregnancy, birth outcomes, and complications and interventions received from medical records. Health facility data, including the location and type of health facility, hospital structure and capacity, and availability of essential and comprehensive obstetric and neonatal healthcare resources, were also obtained for each facility.

Data were collected over a period of 2 months from May 2010 to December 2011 in facilities with ≥6000 annual births and over 3 months in facilities with <6000 annual births. In countries in which less than 3000 births were anticipated, the study period was extended to 4 months in all facilities.

We obtained data on 314 055 women who gave birth. Of the 89 149 women who gave birth to infants weighing at least 500 g and at 22 or more completed weeks of gestation by the time of caesarean section, we excluded 27 (0.2%) because of missing prophylactic antibiotic status, and described our data on 89 122 women. For the multivariate analyses, we further excluded 6808 pregnancies (7.6%) because of missing covariates, and based our results on complete case analysis.

Variables and definitions

The use of prophylactic antibiotics was specifically assessed in the questionnaire. Variability among institutional coverage of antibiotic prophylaxis was explored and categorised into three categories according to the distribution: 'good' (≥90% coverage), 'poor' (50–89% coverage) and 'very poor' (<50% coverage).

Other facility-level information, such as size, location and capacity, was provided by the hospital coordinator through a specific, self-explanatory institutional data collection form. Using data available from this form, we created a 'facility capacity index category' – a proxy for the institution's capacity to provide obstetric care – comprising six areas that reflect the standard of basic services, medical services, emergency obstetric services, laboratory tests, hospital practices and human resources, calculated into a continuous index and categorised as 'good', 'poor' or 'very poor'. The Human Development Index (HDI) based on the 2012 ranking[21] was used as a proxy for the different medical and social backgrounds between countries.

We defined bacterial infection as having any of the following complications identified during pregnancy or up to 7 days postpartum: puerperal endometritis, pyelonephritis, systemic infections including sepsis, and other infections needing therapeutic parenteral antibiotics.

To determine maternal risk factors for the lack of use of prophylaxis, as well as for the absence of bacterial infection, we considered the following variables as exposures at the individual level and further categorised them as shown in Table 1: maternal age at delivery; marital status; educational attainment; parity; previous caesarean section; multiplicity of the pregnancy; major fetal congenital malformation; length of gestation; onset of labour; and maternal complications as follows: severe anaemia, defined as haemoglobin < 7 mg/dl; bacterial infections defined as pyelonephritis, sepsis or other systemic infection; HIV or AIDS; malaria or dengue; chronic hypertension; pre-eclampsia or eclampsia; obstetric bleeding (placenta praevia, accreta/increta/percreta placenta, abruptio placenta, ruptured uterus, postpartum haemorrhage or any other obstetric haemorrhage); and other maternal medical conditions (presence of diseases or injuries affecting the heart, lung, liver or kidneys).