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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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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.

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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%

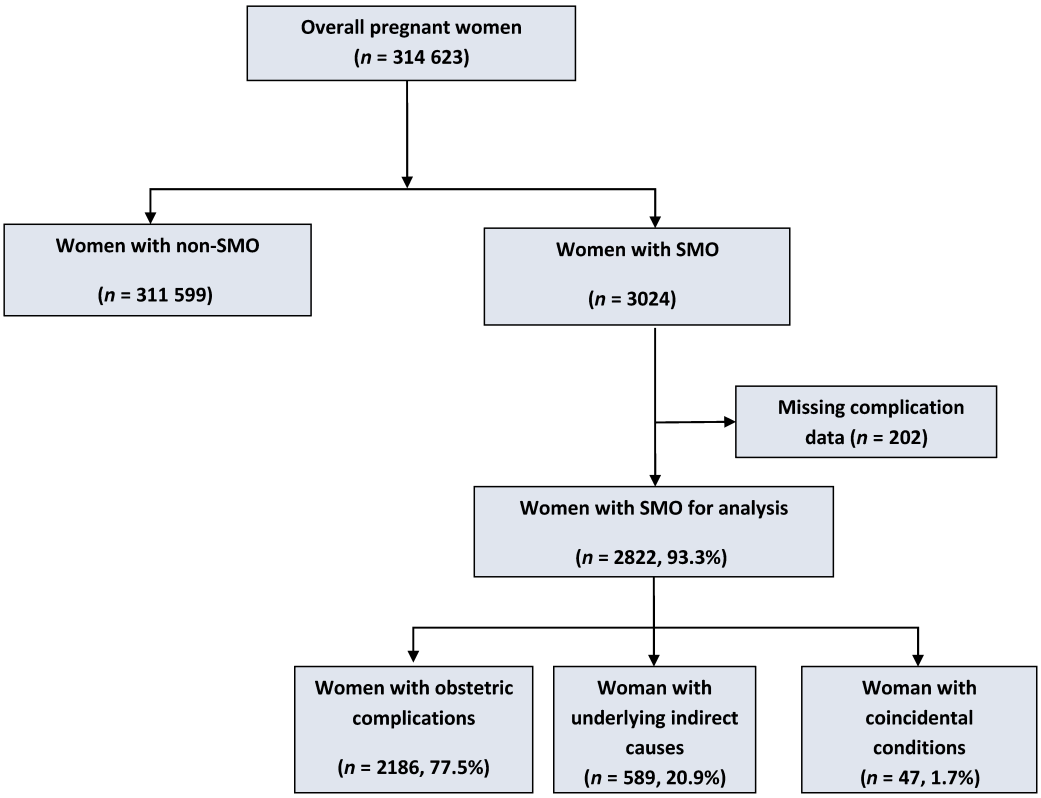

Figure 1. Prevalence of underlying indirect causes in women with severe maternal outcomes.

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)

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,

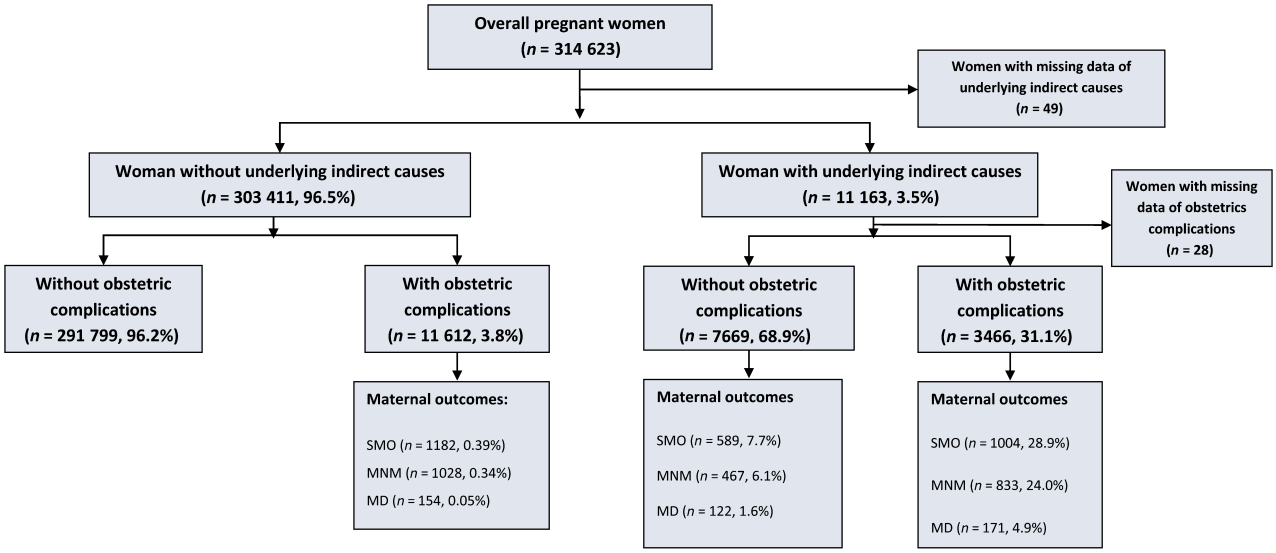

Figure 2. Flow of data for maternal adverse outcomes in women with and without underlying indirect causes.

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

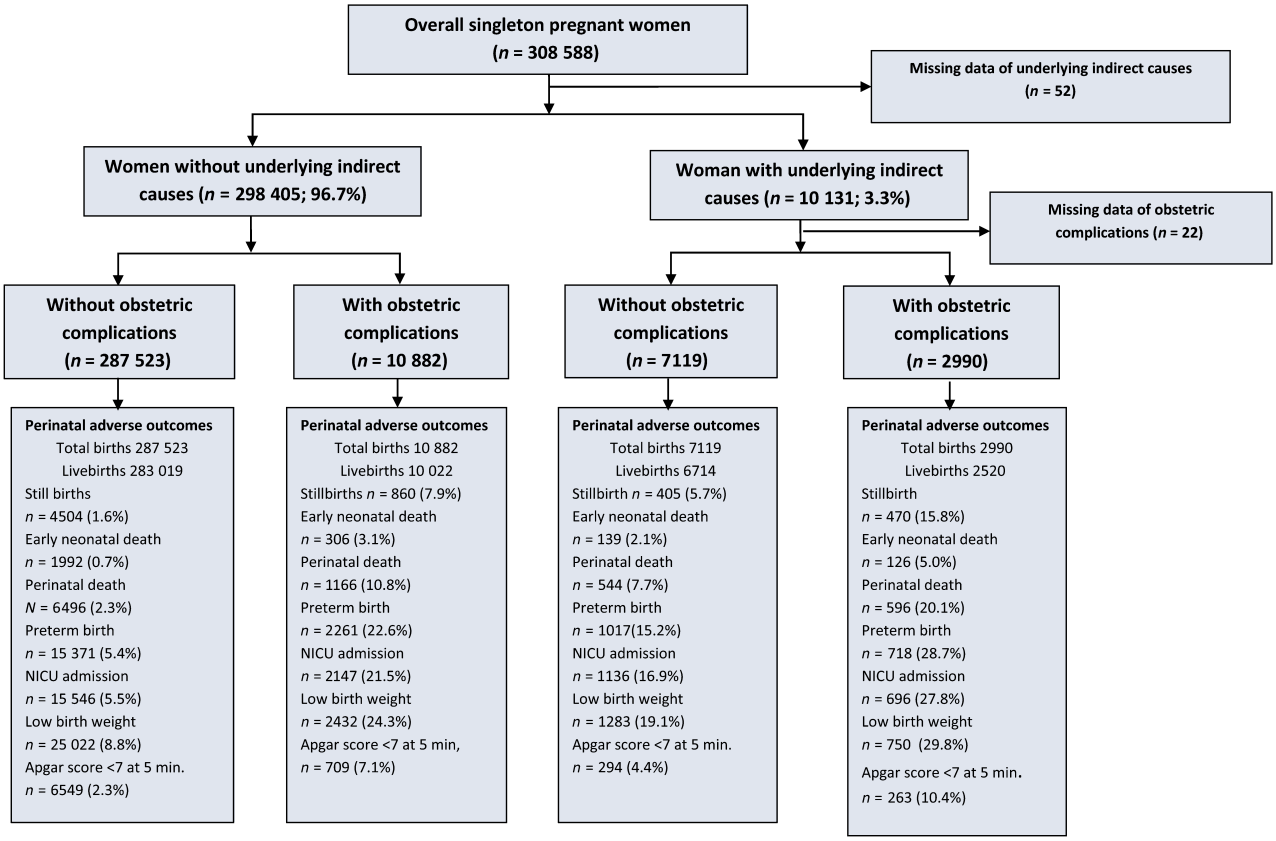

Figure 3. Flow of data for perinatal adverse outcomes in women with and without underlying indirect causes.

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).

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