Received: 12 April 2020 | Revised: 4 August 2020 | Accepted: 5 October 2020

DOI: 10.1002/ijgo.13413

CLINICAL ARTICLE

Obstetrics

WILEY | International Journal of Gynecology & Obstetrics | FIGO

Stillbirths and neonatal deaths among 18 942 women with postpartum hemorrhage: Analysis of perinatal outcomes in the WOMAN trial

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Funding Information
London School of Hygiene & Tropical Medicine; Pfizer; Department of Health; Wellcome Trust; Bill & Melinda Gates Foundation

Abstract

Objective: To describe the rates and risk factors for stillbirth and pre-discharge neonatal mortality (PDNM), and impact on quality of life (QoL) among women with postpartum hemorrhage (PPH).

Methods: A secondary analysis was conducted of the WOMAN trial, which evaluated the use of tranexamic acid for PPH and collected infant outcome data to assess drug safety. The analysis was restricted to singletons (n=18 942). Overall and country-level rates of stillbirth and PDNM were calculated. Multilevel logistic regression models examined the association of stillbirth and PDNM with selected risks, and the association of mother's QoL at discharge after stillbirth or PDNM.

Results: For women with PPH, the rate of stillbirths was 104.42 per 1000 births (n=1978) and the rate of PDNM was 15.56 per 1000 live births (n=264). Cesarean delivery, increasing blood loss, maternal complications, and maternal death were strongly associated with these adverse outcomes. Women with stillbirth and PDNM were significantly more likely to report poorer QoL.

Conclusion: Women with PPH experience an extremely high rate of stillbirth and slightly elevated PDNM, which is associated with markers of the severity of their condition and impacts on their QoL.

KEYWORDS
Neonatal mortality; Postpartum hemorrhage; Stillbirth

1 | INTRODUCTION

Every year there are approximately 0.29 million maternal deaths, 2.6million stillbirths, and 2.5 million neonatal deaths worldwide, the vast majority of which occur in low- and middle-income countries (LMICs).[1–3] Maternal and newborn health and outcomes are intrinsically linked,[4] with maternal risk factors often factoring in poor perinatal outcomes. Postpartum hemorrhage (PPH) is the largest cause of maternal deaths worldwide, contributing to approximately 20% of all maternal deaths.[5,6] Hemorrhage, like other obstetric complications, often occurs alongside stillbirth and neonatal death,[7] yet there has been limited research into this association, particularly in LMICs. Many trials investigating interventions only focus on maternal outcomes.[8] From the woman's perspective, the health and well-being

of her infant is of fundamental importance, and a death has a huge psychological, social, and economic impact.[9] Data on the psychological effects of perinatal death in LMICs are relatively sparse.

The WOMAN trial assessed the role of tranexamic acid (TXA) for the treatment of PPH in 20 060 women in 21 countries,[10,11] which has been incorporated into WHO guidelines.[12] The trial found that administration of TXA significantly reduced death caused by bleeding.[11]

Data were collected on the infant outcomes to assess safety in breastfed infants as TXA can pass via breastmilk in low quantities, and on the mother's quality of life (QoL) for the purpose of cost-effectiveness analyses.[10] The impact of perinatal deaths on mothers was not addressed or reported. Therefore, the aim of the present study was to investigate the burden and impact of perinatal loss among all women with PPH in the WOMAN trial. The main objectives were: (1) to describe the numbers and rates of stillbirth and pre-discharge neonatal mortality (PDNM); (2) to assess the risk factors for stillbirth and PDNM; and (3) to evaluate whether experiencing stillbirth or PDNM is associated with lower reported QoL for women at discharge or 42 days postpartum if still in hospital.

2 | MATERIALS AND METHODS

The present study is a secondary analysis of data from the WOMAN trial, which has been detailed elsewhere.[10,11] The investigators recruited women aged 16 years or older with PPH after a vaginal birth or cesarean delivery.[11] They defined PPH as "clinically estimated blood loss of more than 500ml after vaginal birth or 1000ml after cesarean section or any blood loss sufficient to compromise hemodynamic stability".[11] The analysis was restricted to singleton deliveries. Ethical approval for the WOMAN trial was obtained for each participating site by the local ethics committee. Ethical approval for this secondary data analysis was obtained from the London School of Hygiene & Tropical Medicine MSc Research Ethics Committee on April 20, 2018 (reference 14850).

The main outcomes of the present study were stillbirth, PDNM, and QoL and anxiety or depression at discharge or 42 days postpartum. Stillbirth was defined by the clinician as birth weight, length, and gestational age were not recorded. The stillbirth rate (SBR) was defined as the number of stillbirths per 1000 births. If the infant was born alive but died before discharge this was classified as PDNM. The PDNM rate (PDNMR) was defined as the number of pre-discharge neonatal deaths per 1000 live births. The QoL variables collected in the trial were from the EQ-5D scale, which measures problems with mobility, self-care, usual activities, pain/discomfort, and anxiety/depression on a three-level scale, and was completed by the doctor or midwife.[10,11] The two higher levels of "some problems" and "severe problems" were combined into "any problems" and a composite binary variable was created for participants who registered "any problems" for any category within the EQ-5D. Variables of interest were maternal age, mode of delivery, location of delivery, estimated blood loss, additional maternal complications, and maternal death. All were coded as described in the WOMAN trial, except additional maternal complications, which was represented by a composite binary variable combining organ failure, sepsis, deep vein thrombosis, pulmonary embolism, and myocardial infarction.

SBRs and PDNMRs were calculated for each country that contributed more than 500 patients to the WOMAN trial and were adjusted for clustering by site. The crude association between each risk factor and the defined outcomes was assessed with χ^2 tests. Then, three-level random-intercept logistic regression models were used to account for clustering by site and country and provide adjusted estimates. Likelihood ratio tests (LRTs) were used for the purpose of interpretation of selected covariates on each outcome. All available covariates were not considered in one model, as many were on the causal pathways for other exposures. For example, it is inappropriate to adjust for maternal death when considering the association between additional maternal complications and stillbirth as maternal death could be on the causal pathway between maternal complications and stillbirth if the maternal death happened after delivery. Some variables that were likely to have occurred after the stillbirth (for example, delivery mode), so cannot be temporally associated, were still assessed for association. The additional maternal complications variable was considered as an effect modifier in the regression model testing associations of stillbirth and PDNM with QoL. All analyses were done using STATA v15.1 (StataCorp., College Station, TX, USA).

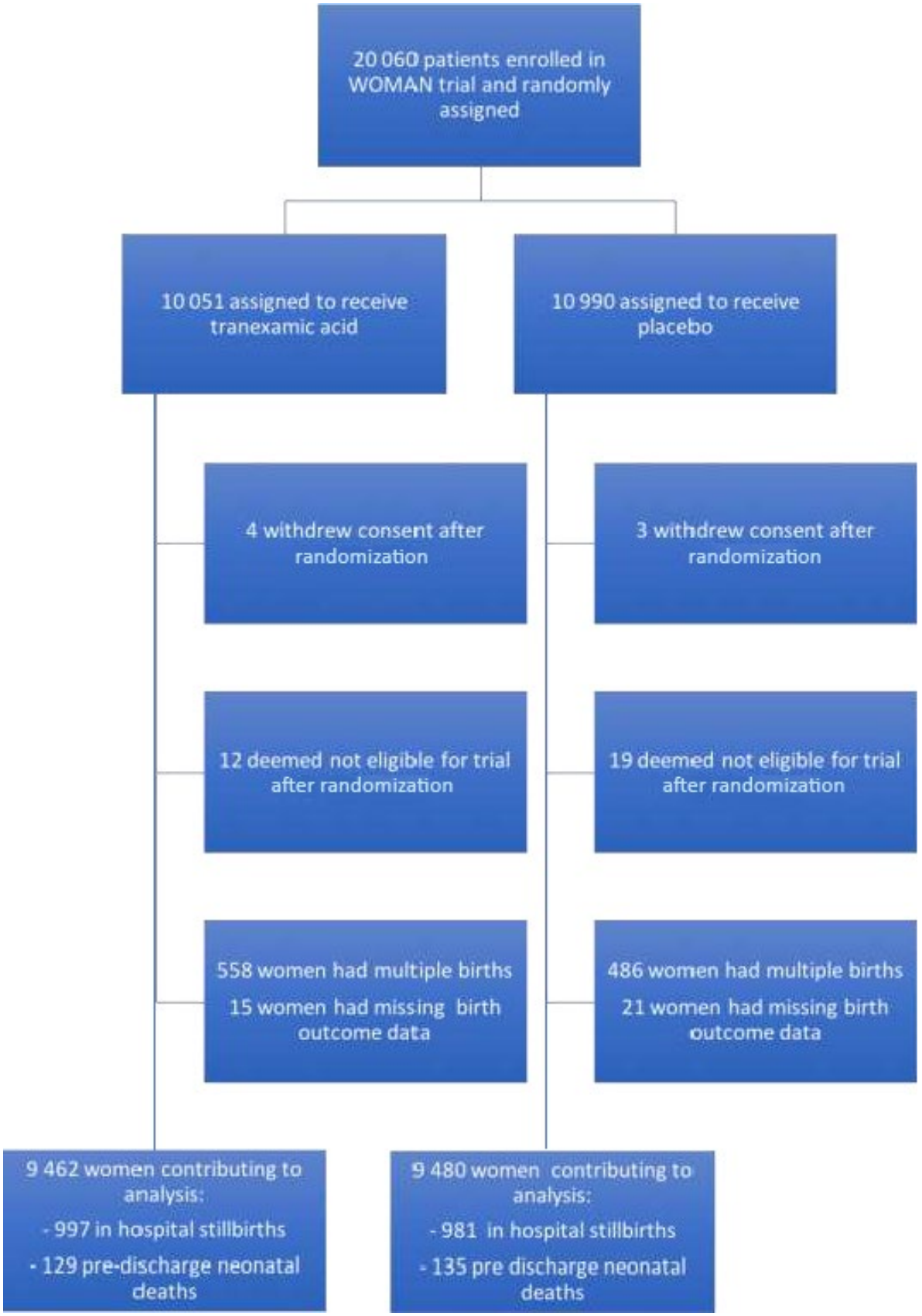
3 | RESULTS

Figure 1 shows the flow of participants from the WOMAN trial. The characteristics of the study participants have been described elsewhere.[11] After excluding those who withdrew consent, were ineligible, had multiple births, or had missing birth outcome data, there were 18 942 women in the dataset. All data were complete or had less than 10 missing datapoints.

There were 455 maternal deaths (2.4%), 1978 stillbirths (10.44%), and 264 pre-discharge neonatal deaths (1.39%). The overall SBR was 104.42 per 1000 births (95% confidence interval [CI] 77.79–138.80). Among the mothers who died, the SBR was 371.43 per 1000 births (95% CI 326.00–419.25) and 97.85 (95% CI 72.71–130.46) among mothers who survived. Figure 2A shows the SBRs in countries that contributed more than 500 patients. Nigeria has the highest point SBR, at 146.51 per 1000 births (95% CI 121.23–175.99), but the CI overlaps with other LMICs.

The overall PDNMR was 15.56 per 1000 live births (95% CI 10.61–22.77) and the median time to discharge among women who survived was 3 days (interquartile range [IQR] 1–4 days). The PDNMR among women who survived was 14.75 per 1000 live births (95% CI 10.36–20.96). The PDNMR among women who died was 62.93 per 1000

FIGURE 1 Flowchart of WOMAN trial and restriction to singleton births for this analysis. Our analyses use data from the WOMAN trial which trialled tranexamic acid in PPH,[11] restricted to singleton deliveries.



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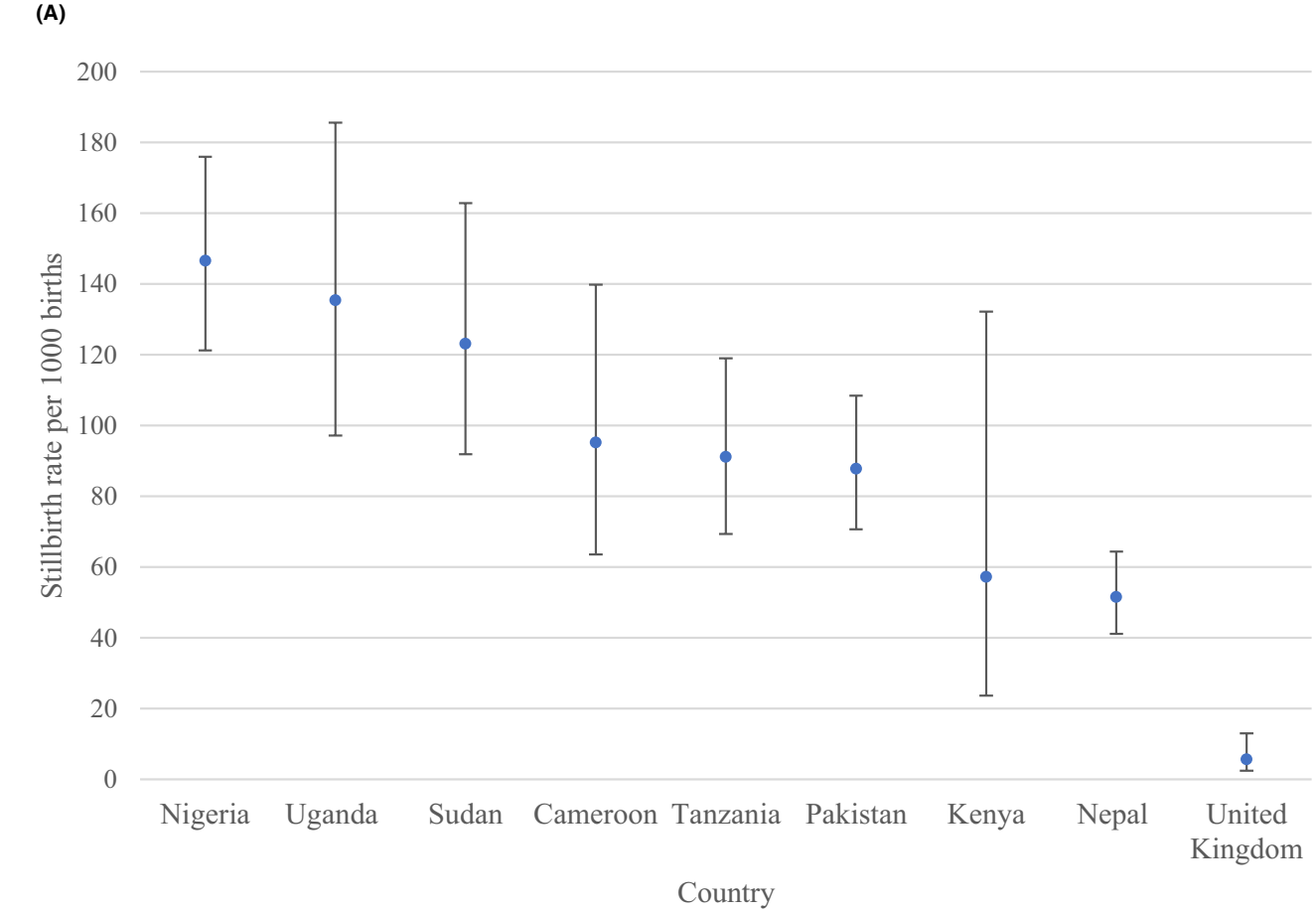
(A)
Stillbirth rate per 1000 births
200
180
160
140
120
100
80
60
40
20
0
Nigeria
Uganda
Sudan
Cameroon
Tanzania
Pakistan
Kenya
Nepal
United Kingdom
Country

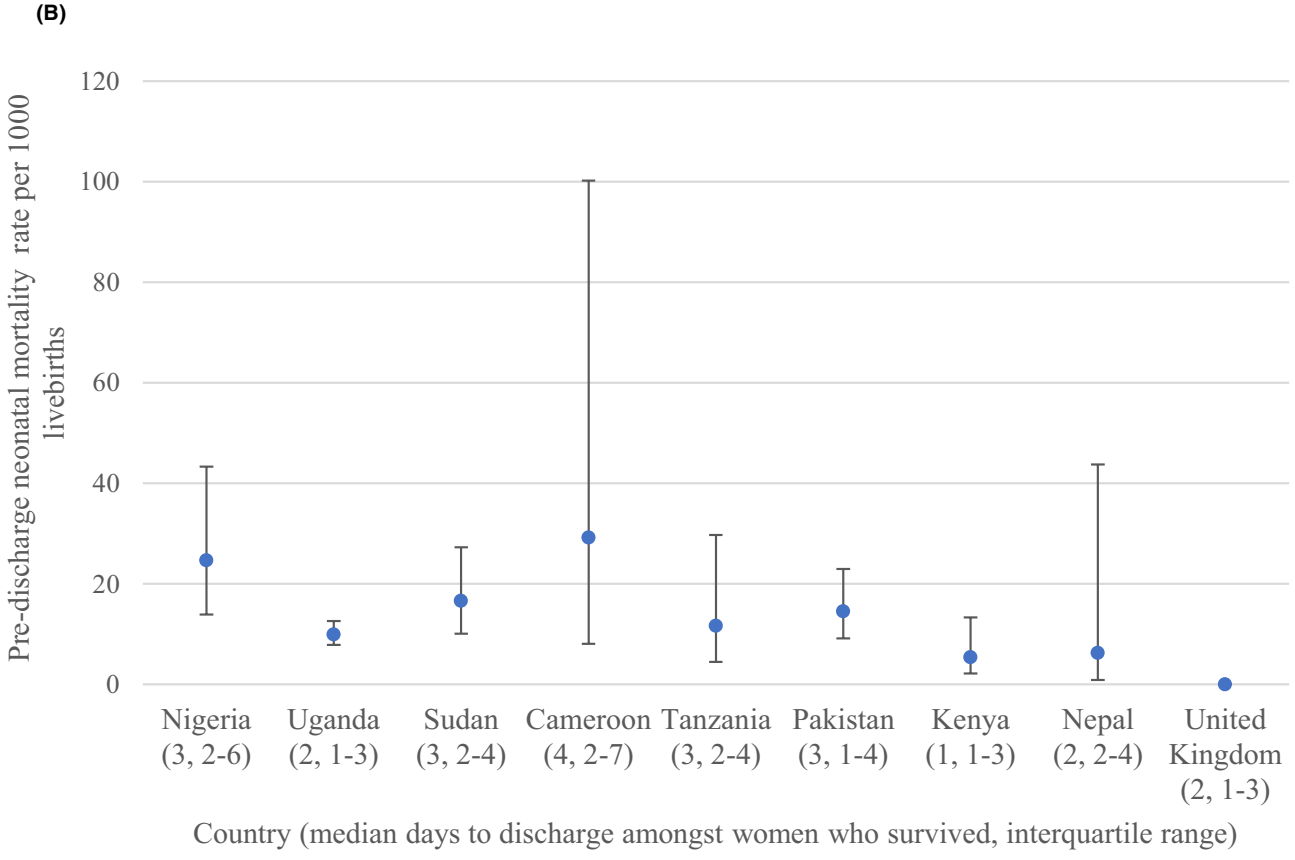
(B)
Pre-discharge neonatal mortality rate per 1000 livebirths
120
100
80
60
40
20
0
Nigeria (3, 2-6)
Uganda (2, 1-3)
Sudan (3, 2-4)
Cameroon (4, 2-7)
Tanzania (3, 2-4)
Pakistan (3, 1-4)
Kenya (1, 1-3)
Nepal (2, 2-4)
United Kingdom (2, 1-3)
Country (median days to discharge amongst women who survived, interquartile range)

FIGURE 2 (A) Stillbirth rates (95% CI) for countries in the WOMAN trial contributing at least 500 patients, adjusted for clustering by site. (B) Pre-discharge neonatal mortality rates (95% CI) in countries in the WOMAN trial that contributed more than 500 patients, adjusted for clustering by site.

live births (95% CI 34.22–112.93) and the median time to death was 0 days (IQR 0–1 days). Figure 2B shows the country-level PDNMRs.

Cameroon had the highest PDNMR, at 29.26 per 1000 live births (95% CI 8.09–100.22). However, Cameroon also had the longest median time to discharge. The CIs also overlap with other LMICs. The PDNMR in the UK could not be estimated as there were no events within the dataset.

Overall, 50.91% of women who had a stillbirth were reported to have a problem with QoL overall compared to 36.53% of women who had a live birth. Of the women who had a pre-discharge neonatal death, 50% were reported to have a problem with QoL. The largest disparity came from the anxiety or depression aspect of the composite variable, where 28.19% of women who had a stillbirth were reported to be anxious or depressed, compared to 8.29% of women with a live birth. Of the women who had a pre-discharge neonatal death, 27.24% were reported to be anxious or depressed.

There is strong evidence of a crude association with all risk factors, apart from delivery location, and the outcomes of stillbirth and PDNM. After adjusting for confounders and clustering (Table 1), there is strong evidence that increasing maternal age, cesarean delivery, increasing estimated blood loss, additional maternal complications, and maternal death are all associated with stillbirth. Increasing estimated blood loss, additional maternal complications, and maternal death are all strongly associated with an increase in the odds of PDNM. Compared with the baseline group of estimated blood loss under 500 mL, women with an estimated blood loss over 1500 mL had around four times the odds of having a stillbirth (odds ratio [OR] 4.03, 95% CI 2.71–5.99), and nearly six times the odds of PDNM (OR 5.74, 95% CI 1.36–24.25).

Table 2 shows the distribution of the overall QoL metric and the subgroup of anxiety or depression across stillbirths and PDNM. There is very strong evidence that both stillbirths and PDNM are associated with problems with maternal QoL and anxiety or depression at discharge or 42 days postpartum. Experiencing either stillbirth or PDNM is associated with approximately two and a half times the odds of having problems with QoL (OR 2.60, 95% CI 2.40–2.95; OR 2.41, 95% CI 1.76–3.29, respectively) and approximately five times the odds of being anxious or depressed (OR 5.56, 95% CI 4.83–6.41; OR 5.08, 95% CI 3.60–7.17, respectively).

There is mixed evidence that additional maternal complications act as an effect modifier (Table 3). The odds of experiencing problems with QoL or anxiety or depression are higher in those that did not suffer additional complications compared to those that did suffer additional complications.

4 | DISCUSSION

The present analyses highlight the huge number of stillbirths (n=1978) and pre-discharge neonatal deaths (n=264) in the WOMAN trial, which had not previously been reported, alongside the 455 maternal deaths. Indeed, there are 1787 more fetal/neonatal deaths than maternal deaths in this trial. The present review of the literature found only three studies that reported on the association between PPH and perinatal outcomes, of which two considered severe hemorrhage, or hemorrhage requiring treatment with a hysterectomy, and none reported stillbirth or early neonatal death rates.[13–15] As well as highlighting this strong epidemiological association of PPH with perinatal death, including a strong dose response pattern, the analyses in the present study show the large, often invisible burden for maternal mental health. The lack of reporting of these perinatal deaths also raises concerns about the visibility and value given to these outcomes.

These 18 942 women with PPH experienced a high mortality for their infants, with an overall SBR of 104.69 per 1000 births (95% CI 77.93–130.93). Given that the global SBR is 18.4,[2] this is an extremely high risk. There are plausible mechanisms that could explain the high rates. Maternal conditions such as pre-eclampsia or other placental conditions lead to increased risks of both PPH and perinatal mortality.[7] Additionally, women in obstructed labor and unable to reach a facility in a timely manner are more likely to suffer both stillbirth and PPH. There is mixed evidence that intrauterine death of the infant can directly cause PPH.[16,17] It has not been established whether the death causes placental change and hemorrhage, or whether the association is due to shared pathologies leading to both outcomes.[17]

A clear dose response relationship was found between increasing estimated blood loss categories and perinatal mortality. It is well documented that increasing blood loss is associated with maternal death, with a "death zone" of over 40% loss[18]; however, associated outcomes for infants are not well studied and it is believed that this is the first time such a dose response has been shown. A systematic review and meta-analysis of the outcomes of emergency peripartum hysterectomy found that of the 128 studies included, only 78 reported on perinatal mortality, and the authors were not able to split into stillbirth and early neonatal death due to differences between the studies.[19]

The findings of the present study underline some known risk factors. Increased maternal age is a recognized risk factor for stillbirth[20] and it was also found that there is an association between maternal age and stillbirth for women with PPH. Cesarean deliveries were also associated with an increase in the odds of stillbirth among women with PPH, but it is difficult to interpret this result as it is possible that the indications for cesarean delivery were reasons associated with stillbirth such as fetal distress or failure to progress, but that there were delays in undertaking the delivery. Some causes of antepartum hemorrhage may continue to cause hemorrhage after delivery, for example placenta previa, which accounted for around 10% of PPH in this population. It is likely that this association is a sign of events preceding the hemorrhage and birth, or events around the time of the birth. This could also be true for the strong association observed between adverse maternal outcomes (additional complications and maternal

TABLE 1 Adjusted ORs from multilevel logistic regression modeling for 18 942 women with PPH in the WOMAN trial regarding selected risk factors.

Risk factors	n (%)	Crude OR (95% CI); *P* value [b]	Adjusted OR[c] (95% CI); *P* value[d], (included confounders)
Stillbirth	1978 (10.44)		
Maternal age (years)		*P*<0.0001	*P*<0.0001 (n=18 935)
<20	59 (6.13)	1.00	1.00
20–24	341 (8.51)	1.42 (1.07–1.89)	1.52 (1.14–2.04)
25–29	585 (10.04)	1.71 (1.29–2.25)	1.77 (1.33–2.35)
30–34	529 (10.82)	1.86 (1.41–2.46)	1.87 (1.40–2.49)
35–39	343 (13.19)	2.32 (1.74–3.10)	2.21 (1.64–2.97)
40+	121 (18.64)	3.51 (2.51–4.91)	3.65 (2.59–5.14)
Mode of delivery		*P*<0.0001	*P*=0.0001 (MA, DL, AMC, MD) (n=18 934)
Vaginal	1330 (9.86)	1.00	1.00
Cesarean	648 (11.87)	1.23 (1.11–1.36)	1.16 (1.03–1.30)
Estimated blood loss (mL)		*P*<0.0001[e]	*P*<0.0001 (MA, DL, MoD) (n=18 933)
≤500	30 (5.14)	1.00	1.00
501–1000	624 (6.70)	1.33 (0.91–1.93)	1.15 (0.78–1.70)
1001–1500	588 (11.03)	2.29 (1.57–3.34)	2.00 (1.34–2.96)
>1500	736 (19.87)	4.58–3.13–6.69)	4.03 (2.71–5.99)
Maternal complications		*P*<0.0001	*P*<0.0001 (MA, DL, MoD) (n=18 934)
Yes	253 (33.86)	4.89 (4.17–5.75)	4.37 (4.68–5.19)
Maternal death		*P*<0.0001	*P*<0.0001 (MA, DL, MoD) (n=18 935)
Yes	169 (37.14)	5.44 (4.47–6.64)	4.43 (3.59–5.45)
PDNM	**264 (1.56)**		
Maternal age (years)		*P*<0.0001[e]	*P*=0.12 (n=16 957)
<20	9 (1.00)	1.00	1.00
20–24	46 (1.25)	1.26 (0.62–2.59)	1.39 (0.66–2.92)
25–29	67 (1.28)	1.29 (0.64–2.59)	1.32 (0.64–2.73)
30–34	77 (1.77)	1.79 (0.89–3.58)	1.73 (0.84–3.58)
35–39	52 (2.30)	2.34 (1.15–4.78)	2.01 (0.96–4.23)
40+	13 (2.46)	2.51 (1.06–5.92)	2.18 (0.89–5.33)
Mode of delivery		*P*=0.0001	*P*=0.14 (MA, EBL, AMC, MD) (n=16 954)
Vaginal	160 (1.32)	1.00	1.00
Cesarean	104 (2.16)	1.66 (1.29–2.13)	1.27 (0.93–1.75)
Estimated blood loss (mL)		*P*<0.0001[e]	*P*<0.0001 (MA, DL, MoD) (n=16 955)
≤500	2 (0.36)	1.00	1.00
501–1000	82 (0.94)	2.63 (0.64–10.71)	1.94 (0.47–8.07)
1001–1500	83 (1.75)	4.91 (1.20–20.05)	3.12 (0.74–13.11)
>1500	97 (3.27)	9.32 (2.29–38.05)	5.74 (1.36–24.25)
Maternal complications		*P*<0.0001	*P*<0.0001 (MA, DL, MoD) (n=16 956)
Yes	37 (7.40)	5.72 (3.98–8.2)	3.85 (2.55–5.82)
Maternal death		*P*<0.0001	*P*=0.0002 (MA, DL, MoD) (n=16 957)
Yes	18 (6.29)	4.49 (2.74–7.35)	3.13 (1.82–5.38)

Abbreviations: AMC, additional maternal complications; CI, confidence interval; DL, delivery location; MA, maternal age; MD, maternal death; MoD, mode of delivery; OR, odds ratio; PDNM, pre-discharge neonatal mortality; PPH, postpartum hemorrhage.

[a]Values are given as number (percentage) or crude/adjusted odds ratio (95% confidence interval).

[b]χ^2 test.

[c]Adjusted for multilevel clustering.

[d]Likelihood ratio test.

[e]χ^2 test for trend.

TABLE 2 Association of mother's QoL and anxiety or depression at time of discharge outcomes with stillbirth and pre-discharge neonatal deaths in the WOMAN trial.[a]

Mortality outcome (stillbirth or neonatal death)	Mother's problems with QoL overall			Mother's anxiety or depression		
	n (%)	Crude OR (95% CI) χ^2 test, *P* value	Adjusted OR[b] (95% CI) LRT, *P* value	n (%)	Crude OR (95% CI) χ^2 test, *P* value	Adjusted OR[b] (95% CI) LRT, *P* value
At birth		*P*<0.0001 (n=18485)	*P*<0.0001 (n=18478)		*P*<0.0001 (n=18485)	*P*<0.0001 (n=18478)
Live birth	6091 (36.53)	1.00	1.00	1383 (8.29)	1.00	1.00
Stillbirth	921 (50.91)	1.80 (1.63–1.99)	2.60 (2.30–2.95)	564 (28.19)	4.34 (3.86–4.89)	5.56 (4.83–6.41)
Pre-discharge		*P*<0.0001 (n=16676)	*P*<0.0001 (n=16669)		*P*<0.0001 (n=16676)	*P*<0.0001 (n=16669)
Alive at discharge	5968 (36.32)	1.00	1.00	1316 (8.01)	1.00	1.00
Neonatal death	123 (50.00)	1.75 (1.35–2.26)	2.41 (1.76–3.29)	67 (27.24)	4.30 (3.23–5.73)	5.08 (3.60–7.17)

Abbreviations: CI, confidence interval; LRT, likelihood ratio test; OR, odds ratio; QoL, quality of life.
[a]Values are given as number (percentage) or crude/adjusted odds ratio (95% confidence interval) (from multilevel logistic regression modeling).
[b]Adjusted for maternal age and additional maternal complications.

death) and stillbirth and PDNM. The strength of the association is clear and while stillbirth would have occurred before the hemorrhage, and the neonatal death may occur after, all these outcomes are likely due to similar underlying pathways, potentially linked to placental pathology. The adverse maternal outcomes may have occurred after the perinatal event so it can only be inferred that they are associated rather than true risk factors.

Maternal mental health is a major, yet understudied, burden, especially in LMICs, and with limited research even in high-income countries. A recent systematic review of the psychological and social impact of stillbirths on parents included 144 studies, of which only 15 were from LMICs and the majority were qualitative.[9] In the mainly LMIC population of the present study, experiencing a perinatal death was strongly associated with a double risk of lower QoL and around five times the risk of anxiety or depression at discharge or 42 days postpartum. There was evidence that the effect of experiencing stillbirth or PDNM on QoL was stronger in women who had not experienced additional complications. This may be because women who had complications were processing their loss in the context of nearly dying themselves. Prost et al.[21] also found an interaction between perinatal loss and problems at delivery on psychological distress. These results suggest that women who had suffered a stillbirth or PDMN with PPH and no other medical complications are being discharged from hospital without their psychosocial needs being met.

TABLE 3 Interaction analysis of the effect of additional maternal complications on the association between stillbirth, and pre-discharge neonatal deaths and mother's QoL and anxiety or depression in the WOMAN trial.[a]

Stratified analysis	Problems with quality of life	Anxiety or depression
Stillbirth		
No additional maternal complications	2.65 (2.33–3.02)	5.90 (5.10–6.82)
Additional maternal complications	1.93 (1.15–3.24)	2.76 (1.73–4.42)
LRT effect modification	*P*=0.24	*P*=0.003
Neonatal mortality		
No additional maternal complications	2.63 (1.91–3.62)	5.75 (4.04–8.19)
Additional maternal complications	0.92 (0.35–2.42)	1.65 (0.59–4.60)
LRT effect modification	*P*=0.05	*P*=0.02

Abbreviations: CI, confidence interval; LRT, likelihood ratio test; OR, odds ratio.
[a]Values are given as odds ratio (95% confidence interval).

Only around one-quarter of women experiencing perinatal loss reported feeling anxious or distressed at discharge, which is lower than other estimates.[22] The EQ-5D was not designed for this purpose and likely underestimated the true proportion of psychological distress. Pre-discharge surveys about quality of care and respectful care have shown underreporting in similar contexts.[23]

The major strength of our analysis is the study size, multi-country reach, and the data quality. The WOMAN trial provided a robust dataset, with low loss to follow-up or missing data. The large sample size enabled for the first time the estimation of the relatively uncommon events of perinatal mortality around the time of birth in a large population of women with PPH.

Misclassification to stillbirth from live birth and early neonatal death may be an issue, as this was left to the clinician's judgment and the infant may not have been assessed carefully for heart rate or resuscitated quickly. There are limitations, for example, confounders to some of the associations were not included in the data collection, such as maternal co-morbidities, delivery details, and sociodemographic characteristics. Additionally, it was not possible to assess QoL after discharge as this was not collected. Since the trial was facility-based, there is selection bias for countries where the percentage of home births remains high.

5 | CONCLUSION

Given that the women with PPH in the present study experienced at least five-fold the average global risk of stillbirth, and that more than 2000 deaths were recorded and not reported in the original reporting of this trial, it is recommended that maternal health studies should also report perinatal outcomes.[24] This is particularly relevant for cost-effectiveness analyses, as including such outcomes will have a major shift in the ratio of effectiveness compared to cost.[25] Importantly, not considering the outcome of a woman's child is also negating her and her family's own ambition that their infant should live and be counted.

ACKNOWLEDGMENTS

The WOMAN trial was funded by the London School of Hygiene & Tropical Medicine, Pfizer, the Department of Health (UK) (grant number HICF-T2-0510-007), the Wellcome Trust (grant number WT094947), and the Bill & Melinda Gates Foundation (grant number OPP1095618). This additional analysis did not receive any specific funding and was undertaken as the MSc summer project of AH. The authors would like to thank all within the WOMAN trial collaborative group, trial sites, and trial investigators, as listed in the primary WOMAN trial publication,[11] and the women who took part in the trial.

AUTHOR CONTRIBUTIONS

JL and HS proposed the idea for the analyses. AH undertook the data analysis with statistical supervision from AK. AH drafted the manuscript with direction from JL. All authors (JL, HS, AH, AK, IR) contributed to the final version of the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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