Lives Saved Tool Technical Note
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Relationship between anemia and maternal mortality in LiST

Is there a risk of maternal mortality due to anemia?

Murray-Kolb and colleagues did a systematic review of anemia and its relationship to maternal mortality for the Child Health Epidemiology Research Group (CHERG) in 2010.[1] The study used a similar approach as was used by Stoltzfus 2001.[2] Overall, the systematic review used a standard approach, with well-defined search terms, use of multiple databases (PubMed, Embase, Web of Science, and Scopus), and had well-defined inclusion and exclusion criteria. Studies had to include measures of hemoglobin and maternal mortality.

The analysis found 10 studies from five countries (Ghana, India, Indonesia, Malaysia, and Nigeria) that met inclusion criteria for the meta-analysis. These included six studies that had been used by Stoltzfus, and four additional studies. The studies and their results are shown in Table 1. All of these were observational studies.

The approach for estimating study effects and for the meta-analysis was to fit a logistic regression model using the midpoint estimate of the range of the hemoglobin level as the independent variable to predict mortality. For all data inputs the unadjusted data sets were used, therefore no control for other risks for mortality such as mothers age, parity, etc.

As with the Stoltzfus review, the meta-analysis found an increased risk for maternal mortality (all causes) by level of anemia. The meta-analysis showed a significant association (OR = 0.713; CI: .596-.852) between a 10 g/L increase in hemoglobin level and maternal mortality.[3]

The Murray-Kolb analysis would yield a relative risk of maternal mortality that is different for different levels of hemoglobin. Using the association, we would have the following relative risks:

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[1] Murray-Kolb L, et al. CHERG Iron Report: Maternal Mortality, Child Mortality, Child Cognition and Estimates of Prevalence of Anemia due to Iron Deficiency. http://cherg.org/publications/iron-report.pdf

[2] Stoltzfus RJ. Iron-deficiency anemia: reexamining the nature and magnitude of the public health problem. Summary: implications for research and programs. *J Nutr* 2001; https://www.ncbi.nlm.nih.gov/pubmed/11160600

[3] Applied DerSimonian & Laird (1986) method to fulfill this meta-analysis. The method allowed heterogeneity of individual effect sizes and took sampling variance into account by using inverse of within-study variance.

Mild anemia (Hb 110-100 g/L), RR= 1.4; low-moderate anemia (Hb 100-90 g/L), RR = 1.97; high-moderate anemia (Hb 90-80 g/L), RR= 2.76; and severe anemia (Hb <50 g/L), RR=7.61.

One weakness of the Murray-Kolb review is the use of observational studies that in most cases do not allow for adjustments for possible confounders. While a few of the studies included in the analysis did include some information on confounders and produced adjusted ORs, Murray-Kolb chose not to use this approach, as most studies did not have adjusted ORs. Furthermore, even in the studies with adjusted ORs there were few data used for this adjustment, and none seemed to be able to adjust for access to healthcare, which could be a major confounder in these observational studies.

Another issue is that the Murray-Kolb results look at overall risk, while other studies have tried to stratify maternal mortality risk by hemoglobin levels. In an analysis using various methods, Brabin et al. 2001[4] found that while there was a strong and significant relationship between maternal mortality and severe anemia (RR = 3.51, 95% CI: 2.05-6.00), there was no significant risk relationship between mild and moderate levels of anemia and maternal mortality. Note that the studies included in this analysis were a sub-set of the six studies used in the Stoltzfus analysis and the Murray-Kolb analysis.

Based on these analyses, we have decided to apply an elevated risk of mortality to only women with severe anemia (<50 g/dL). We believe this is the most appropriate and conservative approach given the data available.

Inputs needed for LiST

Our approach to linking interventions to anemia level and then anemia level to risk of maternal mortality necessitates three sets of inputs. First, we need to have the distribution of hemoglobin levels among pregnant women over time. We now have estimates by country from an analysis led by the WHO.[5] Unfortunately, the surveys are generally small and there are not reliable estimates of severe anemia. Instead, WHO estimates give values of hemoglobin levels down to 70 g/L and below. We will need to develop an approach to estimating percent of pregnant women who have severe anemia.

Second, we need to produce estimates of interventions effectiveness on reducing anemia in terms of changes in hemoglobin levels. This is being done through Heidkamp et al., forthcoming

[4] Brabin BJ, Hakimi M, Pelletier D. An analysis of anemia and pregnancy-related maternal mortality. J Nutr 2001; https://www.ncbi.nlm.nih.gov/pubmed/11160593.

[5] Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. Lancet Glob Health. 2013; 1:e16-25. https://www.ncbi.nlm.nih.gov/pubmed/25103581

part of the LiST *Journal of Nutrition* supplement, and we will use these new estimates of impact on hemoglobin levels in the future.

Finally, we need maternal mortality by cause, so that anemia can be linked to a subset of causes of maternal mortality. In LiST, we use the WHO estimates of maternal mortality by cause. [6]

Each of these will be discussed in further detail below.

Anemia prevalence

The WHO has recently (2014) made estimates of hemoglobin levels for non-pregnant women of reproductive age, pregnant women, and children. These are time trends for all countries from 1990 to 2012. For pregnant women, this analysis provides estimates of the percent of pregnant women (during pregnancy) who have appropriate hemoglobin levels (above 110 g/L), as well as the percent of women who have hemoglobin levels between 110-100, 100-80, 80-70, and below 70 g/L. Currently, the WHO's estimates do not include estimates the percent of pregnant women with severe (below 50 g/L) anemia. It is planned to extend the estimates to this level in the future (2017), but for now we would need to extrapolate the percent of pregnant women with severe anemia.

We used a logit model to estimate the proportion of pregnant women with Hb levels below 50 g/L given the proportion of women at the different Hb levels estimated by the WHO. This resulted in a country-specific estimate of pregnant women who are severely anemic. For all of the low- and middle-income countries, less than 1% of pregnant women fell into the severely anemic category. We will use these estimates of prevalence of severe anemia in women until the WHO produces their next round of estimates, which should include estimates of proportion of pregnant women with severe anemia.

Linking interventions to changes in anemia

The LiST model works by linking scale-up of health interventions to reduction in anemia. Similar to the current model for stunting, as coverage of an intervention increases, the distribution of hemoglobin levels of pregnant women will be altered based on the efficacy of an intervention in terms of changing hemoglobin levels. This will be applied uniformly to the distribution. For example, if we had a new intervention that would increase hemoglobin levels and it was given to all pregnant women who are anemic, then it would shift the entire distribution of these women to the right (higher hemoglobin levels). A second intervention would then apply its efficacy to

[6] Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014; 2:e323-333.

shift the distribution that resulted after applying the first intervention. This ensures that we can estimate the impact of interventions on anemia, by levels of severity.

Linking changes in anemia to maternal mortality

As discussed above, we have decided to apply an elevated risk of mortality only to women with severe anemia (<1% of the population, typically). We will use OR = 10.675 (95% CI: 4.605, 27.763), based on a reanalysis of the data in Murray-Kolb et al., applied only to women with severe anemia. This effect size is on all-cause maternal mortality; however, in LiST we use cause-specific mortality.

LiST uses the WHO estimates of causes of maternal mortality. There are seven specific direct causes of maternal mortality. These are antepartum hemorrhage, intrapartum hemorrhage, postpartum hemorrhage, hypertensive disorders, sepsis, abortion, and embolism. In addition, there is a category for other direct causes (not specified) and a category for indirect causes. These sum to 100% of all maternal deaths.

In order to take a conservative approach, we have decided to link the increased mortality risk of severe anemia only to specific causes of mortality that we believe are linked in a biologically plausible manner to anemia. These are the three types of hemorrhage (antepartum, intrapartum, and postpartum). This would result in less overall effect of reduced anemia on maternal mortality than suggested by the Murray-Kolb and Brabin papers, but would be conceptually appropriate as anemia would only be linked to causes of maternal mortality that are clearly causally related. This approach has been done in the past for other findings (e.g., efficacy of chlorhexidine on all-cause neonatal mortality was applied to neonatal deaths due to sepsis only) and is in line with the CHERG guidelines for evidence review.[7]

Conclusion

Given that the relative risks are based on observational data and anemia levels may well be confounded with other variables such as poverty, access to health care, and low BMI, we believe a conservative estimate is more appropriate. Our recommendation is to use the Murray-Kolb analysis as the basis for the new estimate of OR = 10.675 for pregnant women with hemoglobin levels below 50 g/L (severe anemia). This RR will only be linked to three causes of maternal mortality: antepartum, intrapartum, and postpartum hemorrhage.

[7] Walker N, Fischer-Walker C, Bryce J, Bahl R, Cousens S. Standards for CHERG reviews of intervention effects on child survival. Int J Epidemiol. 2010;39:i21–31. https://www.ncbi.nlm.nih.gov/pubmed/20348122

Table 1: Estimates of odds ratio of maternal mortality associated with a 1 g/dl increase in hemoglobin level, from Murray-Kolb et al.

Study ID	Stoltzfus results	New results
Malaysia 65	0.74 (0.68-0.80)	0.65 (0.59-0.72)
Nigeria 75	0.46 (0.15-1.42)	0.49 (0.18-1.38)
India 80	0.61 (0.57-0.64)	0.56 (0.53-0.60)
Nigeria 82	0.38 (0.83-1.09)	0.43 (0.18-1.02)
Nigeria 85	0.95 (0.83-1.09)	0.95 (0.83-1.09)
India 95	0.84 (0.81-0.88)	0.81 (0.77-0.86)
India 02		0.73 (0.13-0.42)*
Nigeria 03		0.41 (0.04-3.72)*
Ghana 06		0.46 (0.13-1.60)*
Indonesia 08		0.83 (0.71-0.98)
Combined Estimates		
6-study	0.746 ± 0.088 (0.623-0.892)	**DSL (1986)**
10-study		0.698 ± 0.107 (0.566-0.861)
		0.713 ± 0.091 (0.596 -0.852)

Note: * set value of 0.1 for zero death

Odds ratio is calculated as $1/(.713^7) = 10.675$

Figure 1: General structure within LiST for linking interventions to reduce anemia to maternal mortality risk