Poster #803

Mortality Risk Associated with Preterm and SGA Stratified by Maternal HIV Status

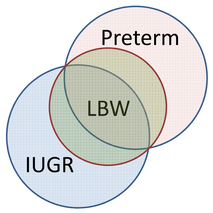
Ayesha Sania (1), Emily Smith (2), Wafaie Fawzi (2)

(1) ICAP, Columbia University Mailman School of Public Health (2) Harvard T. H. Chan School of Public Health

Background

- Neonatal and infant mortality attributed to preterm and Small for gestational age (SGA) are substantial in low and middle income countries.
- Risk of mortality due to preterm and SGA among HIV exposed infants are yet to be estimated.
- Each year, an estimated 32.4 million babies are born SGA, of them 7.5 million in sub Saharan Africa.
- Prevalence of SGA and associated mortality risk varies by the choice of the reference populations.
- Preterm birth and SGA are the underlying biologic conditions leading to low birth weight (LBW)

Figure 1: LBW due to preterm and or IUGR



Objectives

- To examine the association of preterm birth and SGA with neonatal and infant mortality.
- To evaluate effect modification by infants HIV exposure.

Methods

- Study Design: Individual level pooled analyses of five birth cohorts in Tanzania.
- Randomized trials of nutritional supplements
- Study Region:
  Urban- Dar es-Salam (Ilala, Temeke, Kinondoni)
  Rural- Morogoro (Ulanga, Kilosa, and Kilombero)
- Sample Size: 32000 singletons.

Gestational age assessment:

Based on reported date of last menstrual period.

Gestational age category	Definition
Prematurity	<37 weeks
Late prematurity	$34^{0/7}$ to $36^{6/7}$ weeks
Early prematurity	$28^{0/7}$ to $33^{6/7}$ weeks

SGA assessment:

- Birth weight measured up to 10 gram precision by research midwives.
- Small for gestational age (SGA) and appropriate for gestational age (AGA) defined using the intergrowth standard[1].

Size for gestational age	Definition
AGA	Birthweight ≥ 10 th percentile for GA
SGA	Birthweight <10 th percentile for GA
Severe SGA	Birthweight <3rd percentile for GA

Outcome assessment

Outcome	Definition
Neonatal Mortality	Death of a live-born within 28 days
Post-neonatal Mortality	Death of a live-born between 29 to 365 days
Infant Mortality	Death of a live-born within 365 days

Data Analysis:

GA	SGA	AGA
≥ 37 weeks	Term-SGA	Term-AGA (reference group)
< 37 weeks	Preterm-SGA	Preterm-AGA

- Cox proportional hazards models for newborn and infant mortality.
- Kaplan–Meier method for cumulative incidence curves of mortality.
- Log rank test to evaluate effect modification.

Table 1: Description of the pooled studies

Study	Study site	Cohort size	Analyzed cohort size	Follow up period	Maternal HIV status[1]	% LBW[2]	% SGA[3]	% PTB[4]
Fawzi 2007[2]	Dar es Salaam	8430	7401	(12-27 wks of pregnancy) -18 months	Negative	6.7	10.2	15.3
Fawzi 2007[3]	Dar es Salaam	1078	816	(12-27 wks of pregnancy) - 18 months	Positive	11.2	17.5	22.9
Masanja 2015[4]	Dar es Salaam and Morogorro Region	31,999	19367	(0-3 days) - 12 months	Some positive	7.9	19.6	15.4
Duggan 2012[5]	Dar es Salaam	2387	2246	6 wks - 2 yrs	Positive	7.1	20.8	14.2
McDonald 2015[6]	Dar es Salaam	2400	2158	6 wks - 2 yrs	Negative	3.6	7.5	12.7
TOTAL		46294	31988			7.3	16.6	15.3

[1] Among those in the analyzed cohort s
[2] Low birth weight (LBW) defined as <2500 g
[3] Small for gestational age (SGA) defined as weight for age <10th percentile using INTERGROWTH standards
[4] Preterm birth (PTB) defined as <37 weeks

Results

- Neonatal mortality rate =13.4 / 1000 live births.
- Infant mortality rate = 38.8/ 1000 live births.
- Most of the neonatal death occurred within the first 7 days of life.

Table 2: Incidence of preterm, and small for gestational age in study population (n=31,988)

	Total	Urban	Rural	HIV positive	HIV negative
Term-AGA	21854 (68.32)	14477 (70.59)	7377 (64.27)	2045 (63.91)	8887 (73.28)
Preterm-AGA	4820 (15.07)	3213 (15.67)	1607 (14)	504 (15.75)	1694 (13.97)
Term-SGA	5231 (16.35)	2771 (13.51)	2460 (21.43)	634 (19.81)	1531 (12.62)
Preterm-SGA	83 (0.26)	48 (0.23)	35 (0.3)	17 (0.53)	16 (0.13)
AGA	26674 (83.39)	17690 (86.25)	8984 (78.26)	2549 (79.66)	10581 (87.24)
Moderate SGA(3-10%)	2857 (8.93)	1582 (7.71)	1275 (11.11)	364 (11.38)	807 (6.65)
Severe SGA (<3%)	2457 (7.68)	1237 (6.03)	1220 (10.63)	287 (8.97)	740 (6.1)
Low birth weight	2349 (7.34)	1321 (6.44)	1028 (8.96)	269 (8.41)	875 (7.21)

- Proportion of preterm and SGA higher in HIV exposed.
- Proportion of SGA higher in rural area.

Table 3: Mortality Outcomes by Preterm-SGA Category and Birthweight in the Neonatal, Post-neonatal and Infancy periods

	Neonatal (0-28 days)			Post-neonatal (29-365 days)		Infant (0-12 months)	
	Live birth	Death	Hazard Ratio(95% CI)[1] Adjusted[2]	Death	Hazard Ratio(95% CI)[1] Adjusted[2]	Death	Hazard Ratio(95% CI)[1] Adjusted[2]
All infants	31988	430	NA	810	NA	1240	NA
Preterm-SGA category							
Term-AGA	21854	198	*Ref*	470	*Ref*	668	*Ref*
Preterm-AGA	4820	104	2.40 (1.89-3.05)	162	1.63 (1.36-1.95)	266	1.88 (1.63-2.17)
Term-SGA	5231	124	2.70 (2.15-3.39)	177	1.54 (1.29-1.83)	301	1.94 (1.69-2.23)
Preterm-SGA	83	4	5.32 (1.97-14.35)	1	0.50 (0.07-3.58)	5	1.98 (0.82-4.78)
Birthweight							
≥2500 g	29639	298	*Ref*	701	*Ref*	999	*Ref*
<2500 g	2349	132	5.72(4.65-7.04)	109	2.08(1.70-2.55)	241	3.25(2.82-3.74)

[1]Hazard Ratios and 95% CIs were obtained from Cox proportional hazards models
[2]Adjusted for maternal age, education, parity, type of delivery, location of birth, HIV exposure, and household wealth

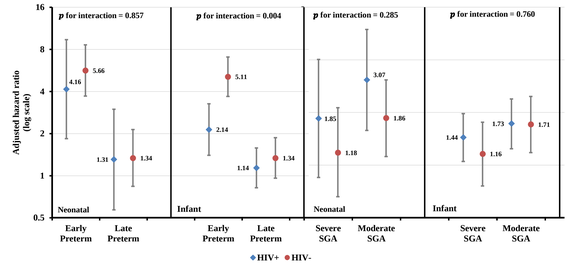
Table 4: Mortality Outcomes by Gestational Age, and SGA Category in the Neonatal, Post-neonatal and Infancy periods

	Neonatal (0-28 days)			Post-neonatal (29-365 days)		Infant (0-12 months)	
	Live birth	Death	Adjusted Hazard Ratio (95% CI)[1,3]	Death	Adjusted Hazard Ratio (95% CI)[1,3]	Death	Adjusted Hazard Ratio (95% CI)[1,3]
All infants	31988	430	NA	810	NA	1240	NA
Gestational Age							
≥37 wks	27085	322	*Ref*	647	*Ref*	969	*Ref*
34 to <37 wks	3853	66	1.45(1.11-1.89)	107	1.19(0.97-1.46)	173	1.28(1.09-1.51)
<34 wks	1050	42	3.27(2.37-4.52)	56	2.50(1.90-3.28)	98	6.79(4.86-9.50)
Size for Gestation							
≥10%	26674	302	*Ref*	632	*Ref*	934	*Ref*
3-<10%	2857	55	1.74 (1.29-2.32)	97	1.37(1.11-1.70)	152	1.66(1.18-2.33)
<3%	2457	73	2.70(2.09-3.49)	81	1.36(1.08-2.72)	154	3.27 (2.38-4.52)

[1]Hazard Ratios and 95% CIs were obtained from Cox proportional hazards models
[2]Adjusted for maternal age, education, parity, type of delivery, location of birth, HIV exposure, and household wealth

- Risk associated with preterm and SGA was elevated throughout infancy.
- Greater risk for early preterm and severe SGA.

Figure 2: Risk ratio of neonatal and infant mortality for preterm and SGA severity, stratified by maternal HIV status



- Maternal HIV status modified the risk associated early preterm birth and mortality.
- High mortality (97/1000 live birth) among HIV exposed term infants.

Strenghts and Limitations

- Data from large clinical trials collecting quality data throughout infancy
- Among the early studies to apply intergrowth standard
- Gestational age estimate based on LMP recall.
- Selection bias due to missing birthweight and gestational age.
- Missing HIV status for some pregnant women.

Conclusions

- Prevalence of SGA is lower using the intergrowth standard, but the magnitude of risk of mortality remain similar.
- Interventions targeting preterm and SGA births will substantially reduce infant mortality irrespective of infants HIV exposure.

References

1. Papageorghiou, A.T., et al., *International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project.* Lancet, 2014. **384**(9946): p. 869-79.
2. Fawzi, W.W., et al., *Vitamins and perinatal outcomes among HIV-negative women in Tanzania.* N Engl J Med,
3. Fawzi, W.W., et al., *Multivitamin supplementation improves hematologic status in HIV-infected women and their children in Tanzania.* Am J Clin Nutr, 2007. **85**(5): p. 1335-43.
4. Masanja, H., et al., *Effect of neonatal vitamin A supplementation on mortality in infants in Tanzania (Neovita): a randomised, double-blind, placebo-controlled trial.* Lancet, 2015. **385**(9975): p. 1324-32.
5. Duggan, C., et al., *Multiple micronutrient supplementation in Tanzanian infants born to HIV-infected mothers: a randomized, double-blind, placebo-controlled clinical trial.* Am J Clin Nutr, 2012. **96**(6): p. 1437-46
6. McDonald, C.M., et al., *Daily Zinc but Not Multivitamin Supplementation Reduces Diarrhea and Upper Respiratory Infections in Tanzanian Infants: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial.* J Nutr, 2015. **145**(9): p. 2153-60.

Acknowledgement:

Ayesha Sania is supported by *National Institute of Allergy & Infectious Diseases of the National Institutes of Health under award number T32AI114398*

Emily Smith Sania is supported by *National Institute of Allergy & Infectious Diseases of the National Institutes of Health under award number* T32AI007358