Two Doses of Antepartum Betamethasone reduces airway complications in neonates compared to 1 dose in 32-36 week population.

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Background and Hypothesis

- Antenatal betamethasone reduces neonatal respiratory morbidity; but the benefit of one vs two doses of betamethasone remains in question.[1]
- Furthermore, little research has been done to characterize the interval dose-exposure for betamethasone and delivery.
- The goal of this study is to characterize the effect of second betamethasone dose on neonatal outcomes as time-dependent with distinct dose-timing phenotypes.

1. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. *New England Journal of Medicine*. 2016;374(14):1311-1320. doi:10.1056/NEJMOA1516783;WGROUP:STRING:MMS

Study Design and Methods

Study Population

- Mount Sinai Hospital (MSH) Jan 2013-Dec 2023

Inclusion Criteria: Antenatal betamethasone (1 vs 2 doses), preterm delivery < 37 weeks at MSH

- Exclusion Criteria >2 doses, delivery outside MSH, GA > 37 weeks, IUFD, >14 days from last dose to delivery

Exposure (time from betamethasone (1 vs 2 doses) to delivery

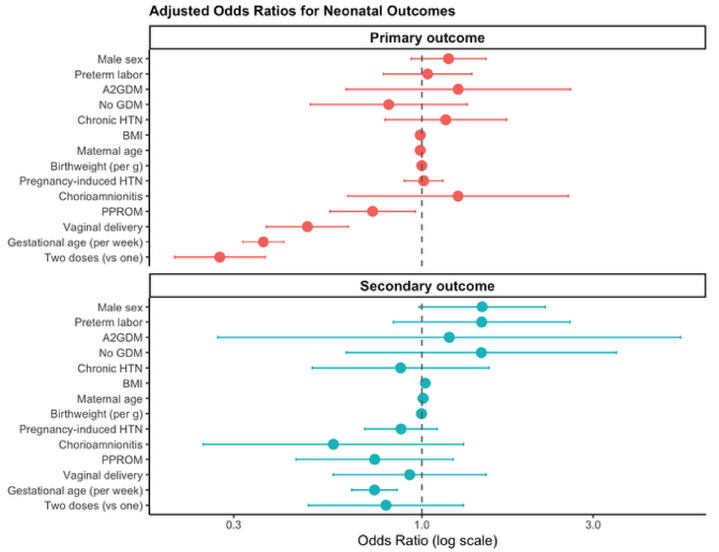
- Primary outcome: composite respiratory morbidity (TTN, RDS, CPAP > 12hrs, O2 > 24hrs, intubation, surfactant)
- Secondary outcome: Composite severe morbidity (IVH, PVL, ROP, NEC, BPD, sepsis)

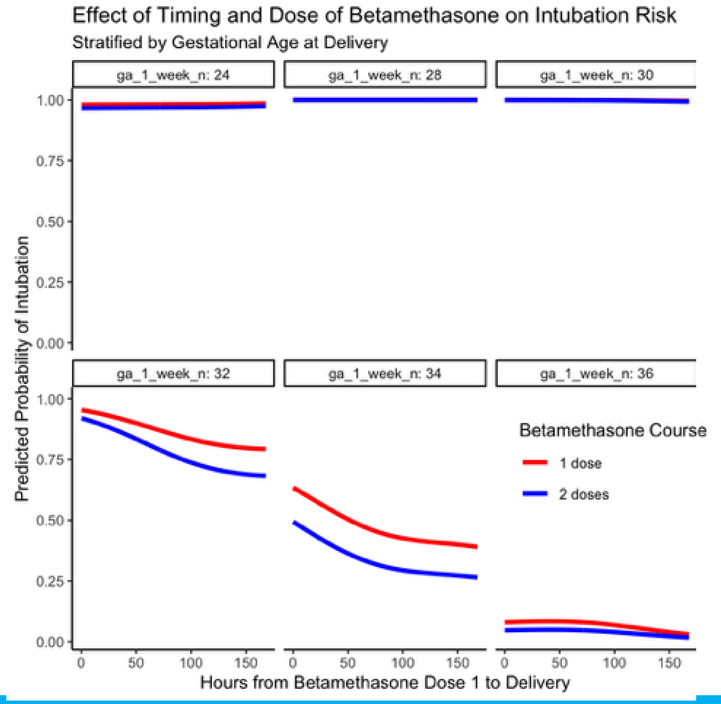
Statistical Analysis

- Logistic regression, nonlinear exposure, dose+timing, Marginal RDs: 1 vs 2 doses at 12h, 24h, 48h, 72h, >72h. Adjusted for GA, birthweight, sex, PTL, PPROM, chorio

Results

- A total of 2,086 mothers and neonates were analyzed, 873 received one dose and 1,266 received two doses of betamethasone. Of the mothers who received two doses, 53 of them received betamethasone <= 2hours before delivery.
- Compared to one dose, two doses were associated with lower respiratory morbidity when delivery occurred shortly after exposure (RD_{12h} = -11.3%, RD_{24h} = -7.3%, RD_{48h} = +1.1%, RD_{72h} = +6.6% and $RD_{>72h}$ +10.2%, $p < 0.05$). For secondary severe neonatal morbidity outcome, no significant dose-timing interaction was observed, and risk differences were small across all exposure times ($p = 0.68$).
- Upon gestational age (GA) subgroup analysis, no significant primary outcome difference was observed until 32 weeks with no difference after 36 weeks. Thus, a 32-36 week sub cohort of 1,493 deliveries (722 received one dose, 771 received two doses of betamethasone) was created and analyzed, demonstrating the two-dose group having significant lower risk of the primary composite outcome across all refit-bootstrap estimates.
- Absolute risk reduction approximately 14-16% lower than the one dose group from 12 to > 72 hours ($p<0.001$). However, no significant association was observed between dose number and secondary composite between one and two doses (ARR < 0.6% across all times).





Conclusions

- This is one of the largest studies demonstrating the benefit of betamethasone as a dose-timing phenotype. Globally across this patient population, a second dose confers benefit only if delivery occurs soon after exposure, with diminishing and potentially adverse associations as intervals increase beyond 48 hours.
- However, when selecting for the 32-36 week population based on the landmark analysis, two doses of betamethasone were associated with a clinically and statistically significant reduction in the primary composite outcome, but not the secondary across all time points.
- Although the initial analysis suggested a dose-dependent response, with the 32-36 week subgroup, the observed association is not simply a function of longer time exposure persisting across the flexible spline, but does suggest additional pulmonary maturation benefits in this population.
  - This could possibly be explained by late-preterm fetuses having sufficient baseline lung maturity that partial corticosteroid exposure (1 dose) is necessary but insufficient to achieve maximal benefit, whereas a two-dose regimen may provide additional pulmonary maturity.
  - Conversely more mature neonates approaching term have marginal benefits. Very early neonates globally have high respiratory morbidity despite full dosing.

Thank you!