# Association Between Prophylactic L-Arginine Supplementation and Risk of Retinopathy of Prematurity and Long-Term Visual Outcomes in Preterm Infants Born Before 29 Weeks' Gestation


A Lodha[1], M. Munro[2,3], M. Kamaluddeen[2,4] A. Ambikumar[2,3], N. Carrell[2,5], A. Benlamri[2,4], O. Srivastava[1], P. Mitchell[2,3]

[1]Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada. [2]Alberta Health Services, Calgary, Alberta, Canada. [3]Section of Ophthalmology, Department of Surgery, Cummings School of Medicine, University of Calgary, Calgary, Alberta, Canada. [4]Department of Pediatrics, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada. [3]Alberta Health Services, Calgary, Alberta, Canada. [5]Chinook Regional Hospital, Lethbridge, Alberta, Canada.


## Background

- Retinopathy of prematurity (ROP) is common among very preterm infants.
- L-arginine is a potent vasodilator that may modulate retinal vascular responses.
- In preterm infants, prophylactic supplementation with L-arginine has been shown to reduce the incidence of necrotizing enterocolitis (NEC). However, its role in reducing the risk of retinopathy of prematurity (ROP) in preterm infants is not well studied.

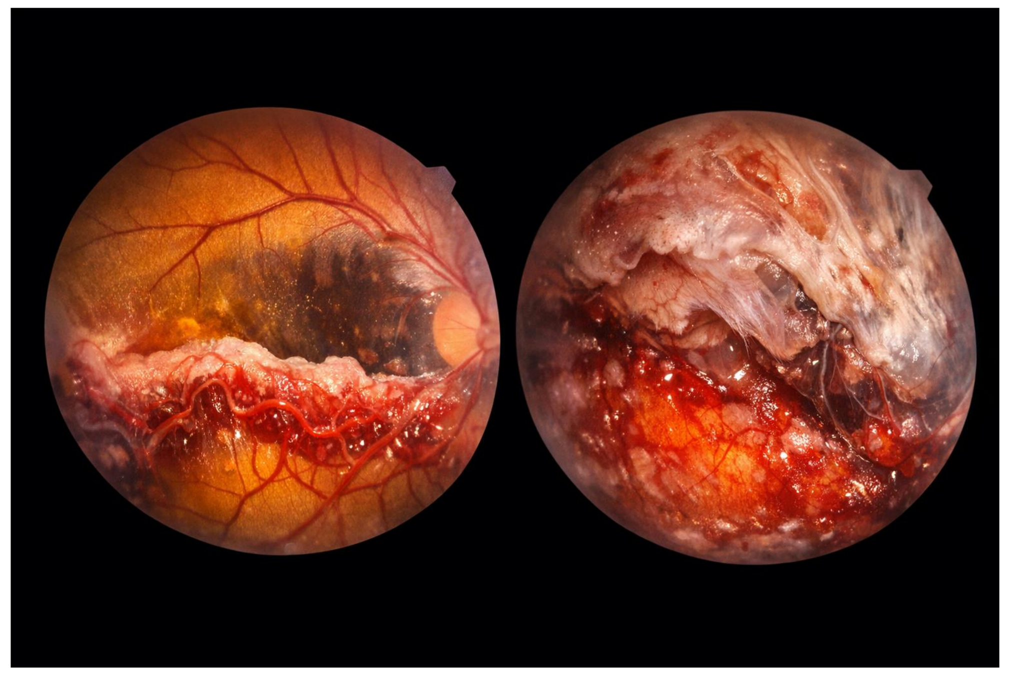
## Objective

To explore the association between prophylactic supplementation of L-arginine and the risk of ROP before discharge, as well as visual outcomes up to 3 years of age, in preterm infants born before 29 weeks' gestational age (GA) and cared for in the NICU.

## Methods

- **Cohort**: Infants born at <29 weeks GA and admitted to Foothills Medical Centre (FMC), Calgary, between August 1999 and May 2007
- **Groups**: Routine arginine supplementation was introduced in April 2003. Cohort was split into 2 groups:
  - Aug 1999 – Mar 2003 (pre-arginine supplementation)
  - Oct 2003 – May 2007 (post-arginine supplementation)

  with Apr 2003-Sep 2003 considered a washout period
- **Primary Outcome**: Any ROP stage ≥ I
- **Secondary Outcomes**: Severe ROP stage ≥ III or treatment, visual impairment or blindness, strabismus or nystagmus diagnosed up to age 3
- **Statistical Analysis**: T-test or Mann-Whitney U test for continuous variables, chi-square or Fisher's exact test for categorical variables, and logistic regression



## Results

**Figure 1. Population flow diagram**

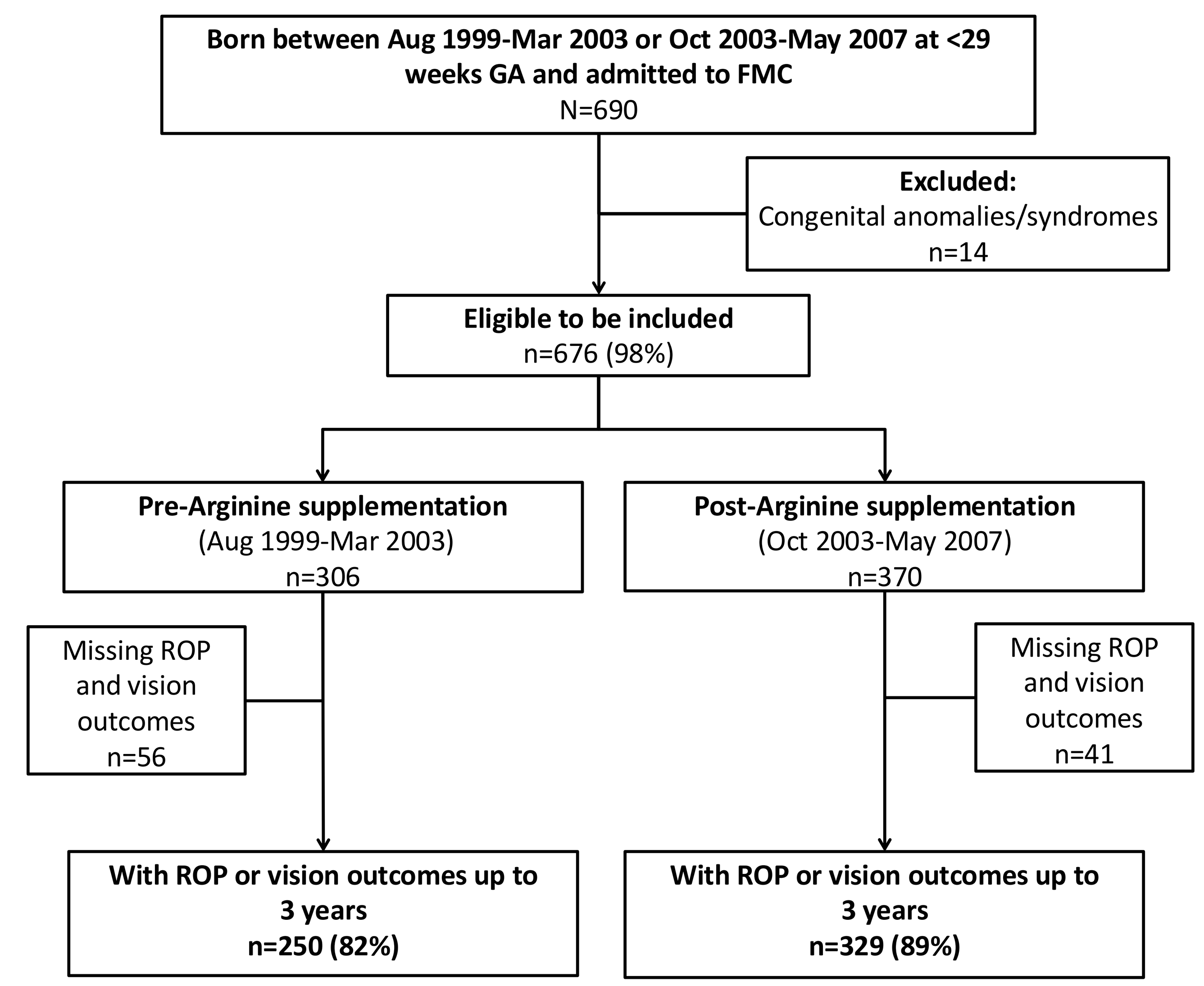



**Table 1. Maternal and neonatal characteristics**

| Characteristic | Pre-Arginine Supplementation (n=306) | Post-Arginine Supplementation (n=370) | p-value |
|---|---|---|---|
| **Maternal characteristics** | | | |
| Maternal age (years), mean (SD) | 30 (6) | 29 (6) | 0.128 |
| Primiparous, n/N (%) | 145/296 (49) | 188/365 (52) | 0.519 |
| Chorioamnionitis, n/N (%) | 21/285 (7) | 86/358 (24) | <0.001 |
| Cesarean delivery, n/N (%) | 165/304 (54) | 200/369 (54) | 0.984 |
| Antenatal corticosteroids, n/N (%) | 238/292 (82) | 308/360 (86) | 0.164 |
| Antenatal antihypertensives, n/N (%) | 32/288 (11) | 44/359 (12) | 0.653 |
| **Neonatal characteristics** | | | |
| Gestational age at birth (wks), mean (SD) | 26.0 (2) | 26.2 (2) | 0.022 |
| Birth weight (g), mean (SD) | 839 (221) | 903 (233) | <0.001 |
| SGA <10th centile, n/N (%) | 27/306 (9) | 28/370 (8) | 0.552 |
| Five-minute Apgar score <7, n/N (%) | 103/303 (34) | 97/363 (27) | 0.041 |
| Resuscitation requiring intubation, n/N (%) | 258/306 (84) | 190/370 (51) | <0.001 |
| Male, n/N (%) | 170/306 (56) | 207/370 (56) | 0.919 |
| Inborn delivery, n/N (%) | 261/306 (85) | 306/370 (83) | 0.362 |
| Multiple birth, n/N (%) | 91/306 (30) | 97/370 (26) | 0.309 |
| Duration of total parenteral nutrition (days), median (IQR) | 17 (16) | 18 (16) | 0.005 |
| Postnatal steroids, n/N (%) | 78/306 (25) | 25/370 (7) | <0.001 |
| Caffeine, n/N (%) | 222/306 (73) | 314/370 (85) | <0.001 |
| Nitric oxide, n/N (%) | 11/305 (4) | 20/370 (5) | 0.267 |
| Respiratory distress syndrome, n/N (%) | 255/306 (83) | 344/368 (93) | <0.001 |
| Need for mechanical ventilation, n/N (%) | 274/306 (90) | 340/369 (92) | 0.241 |
| ≥1 Blood transfusion, n/N (%) | 257/305 (84) | 264/367 (72) | <0.001 |
| Culture positive sepsis, n/N (%) | 67/305 (22) | 63/367 (17) | 0.117 |
| NEC stage ≥2, n/N (%) | 31/306 (10) | 26/370 (7) | 0.148 |
| IVH grade III/IV, n/N (%) | 36/304 (12) | 42/369 (11) | 0.853 |
| Severe neurological injury, n/N (%) | 39/304 (13) | 43/369 (12) | 0.643 |
| Bronchopulmonary dysplasia, n/N (%) | 192/226 (85) | 207/282 (73) | 0.002 |
| Length of hospital stay (days), median (IQR) | 85 (30) | 83 (33) | 0.135 |

## Results continued

**Figure 2. Outcomes before and after routine arginine supplementation**

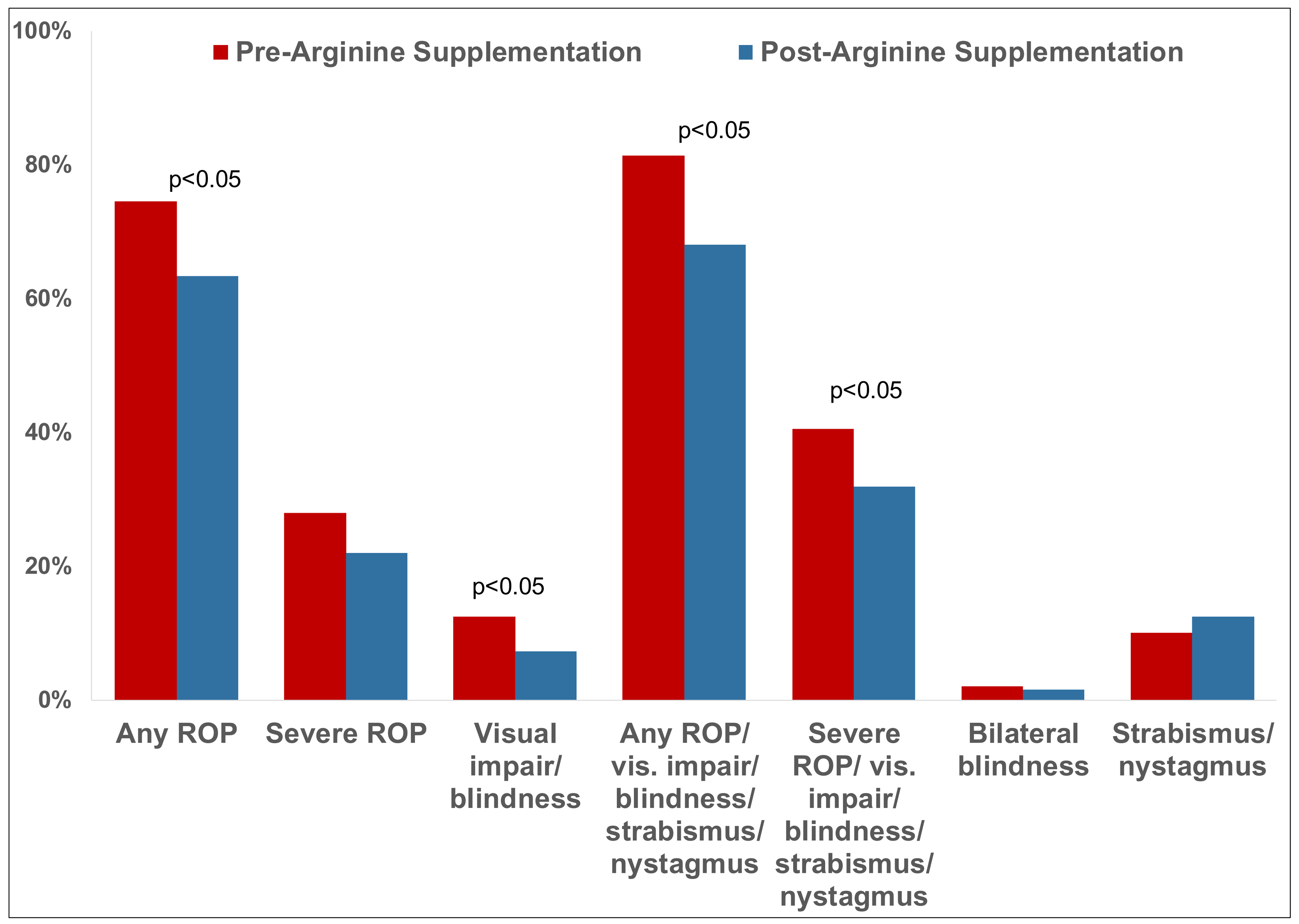



**Table 2. Adjusted odds ratios (OR), Propensity matched OR and 95% confidence intervals (CI) for outcomes post- vs. pre- arginine supplementation**

| Outcome | Adjusted OR* (95% CI) Group II vs. I | Propensity matched** Matched OR (95%CI) Group II vs. I |
|---|---|---|
| **Short term vision outcomes** | | |
| Any ROP | 0.48 (0.28-0.81) | 0.62 (0.40-0.96) |
| Severe ROP | 0.64 (0.37-1.07) | 0.62 (0.38-1.02) |
| **Vision outcomes up to age 3** | | |
| Visual impairment/blindness or strabismus/nystagmus | 0.59 (0.29-1.18) | 0.64 (0.31-1.32) |
| Any ROP or visual impairment/blindness or strabismus/nystagmus | 0.37 (0.20-0.64) | 0.49 (0.30-0.81) |
| Severe ROP or visual impairment/ blindness or strabismus/nystagmus | 0.56 (0.34-0.91) | 0.65 (0.41-1.03) |
| Strabismus or nystagmus | 1.46 (0.72-3.01) | 1.12 (0.57-2.21) |
| Bilateral Blindness | n/a | 0.77 (0.17-3.55) |

*Adjusted for: gestational age, birth weight, sex, cesarean delivery, antenatal corticosteroids, APGAR scores <7 at 5 minutes, small for gestational age (SGA), chorioamnionitis, necrotizing enterocolitis (NEC), severe neurological injury (IVH grade 3 ± periventricular leukomalacia), BPD, ≥1 blood transfusions.

**Propensity score estimated using a logistic regression model using gestational age, sex, cesarean delivery, antenatal corticosteroids, APGAR scores <7 at 5 minutes, SGA, chorioamnionitis, NEC, severe neurological injury, BPD, ≥1 blood transfusion. There were 184 matched pairs in each group. In order to achieve covariate balance between groups, a caliper width of 0.1 SD of the logit of the propensity score was used.

## Conclusions

In infants born <29 weeks gestation, routine L-arginine supplementation was associated with a reduction in ROP but not a statistically significant reduction in severe ROP. At 3 years CA, the risk of visual impairment and/or blindness was reduced in the post-L-arginine supplementation group, but this was not statistically significant after adjusting for confounders.