# Aspiration or Illusion?

## *Improving Survival Outcomes for HLHS*

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# Disclosures

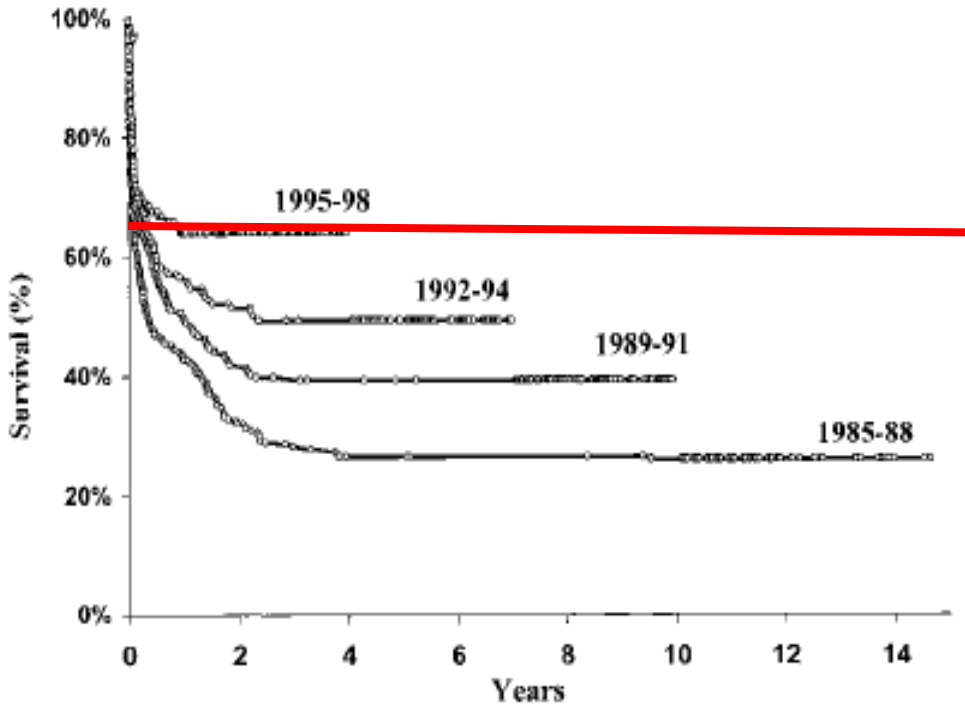
**Conflicts:** None

**Off-label Use:** None

# Survival After Reconstructive Surgery for Hypoplastic Left Heart Syndrome

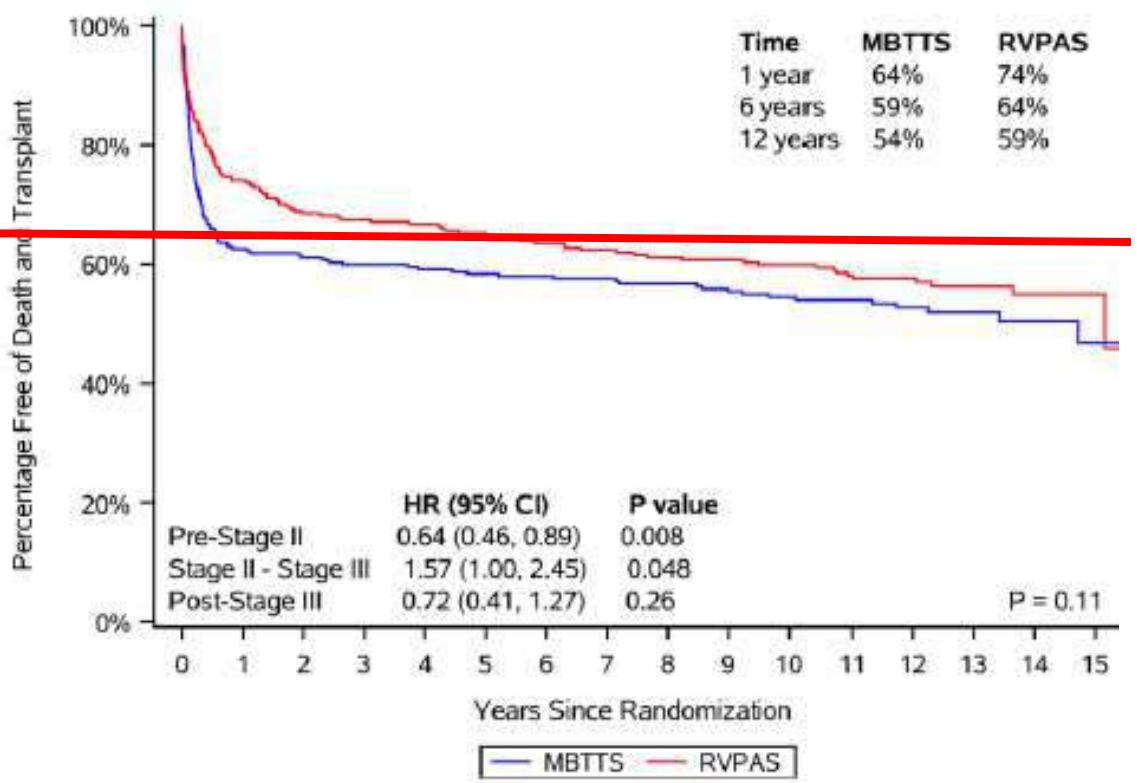
## A 15-Year Experience From a Single Institution

William T. Mahle, MD; Thomas L. Spray, MD; Gil Wernovsky, MD; J. William Gaynor, MD; Bernard J. Clark III, MD



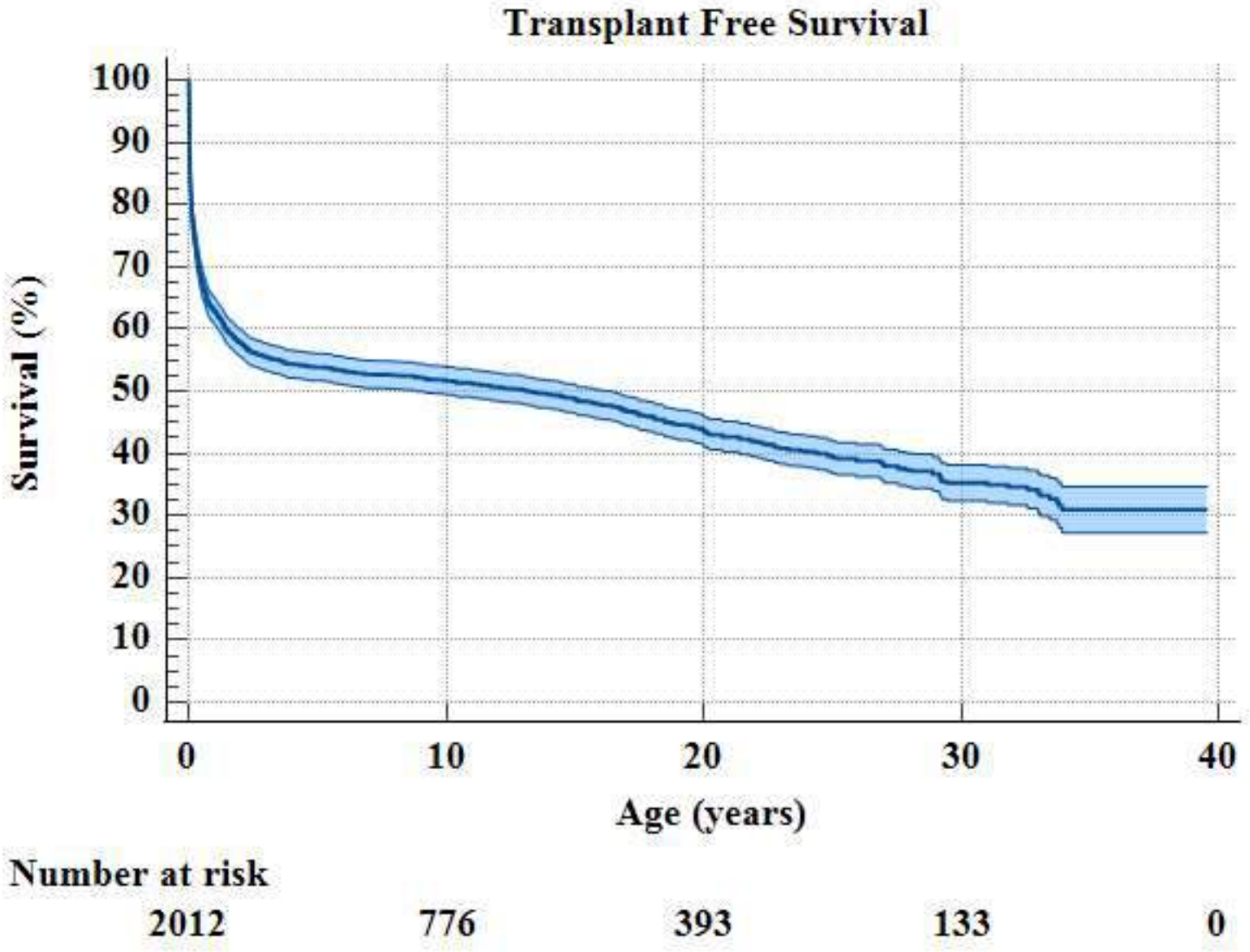

# Longitudinal Follow-Up of Children With HLHS and Association Between Norwood Shunt Type and Long-Term Outcomes: The SVR III Study

Caren S. Goldberg, MD, MS; Felicia Trachtenberg, PhD; J. William Gaynor, MD; William T. Mahle, MD; Chitra Ravishankar, MD; Steven M. Schwartz, MD, MS; James F. Cnota, MD; Richard G. Ohye, MD; Russell Gongwer; Michael Taylor, MD; Stephen Paridon, MD; Peter C. Frommelt, MD; Katherine Afton, BS; Andrew M. Atz, MD; Kristin M. Burns, MD; Jon A. Detterich, MD; Kevin D. Hill, MD, MS; Antonio G. Cabrera, MD; Alan B. Lewis, MD; Christian Pizarro, MD; Amee Shah, MD; Binu Sharma, MS; Jane W. Newburger, MD; on behalf of the Pediatric Heart Network Investigators



# Long-term Survival after Reconstructive Surgery for HLHS

Between 1/1/1984 and 12/31/2023, **2012** neonates underwent reconstructive surgery for HLHS at CHOP.

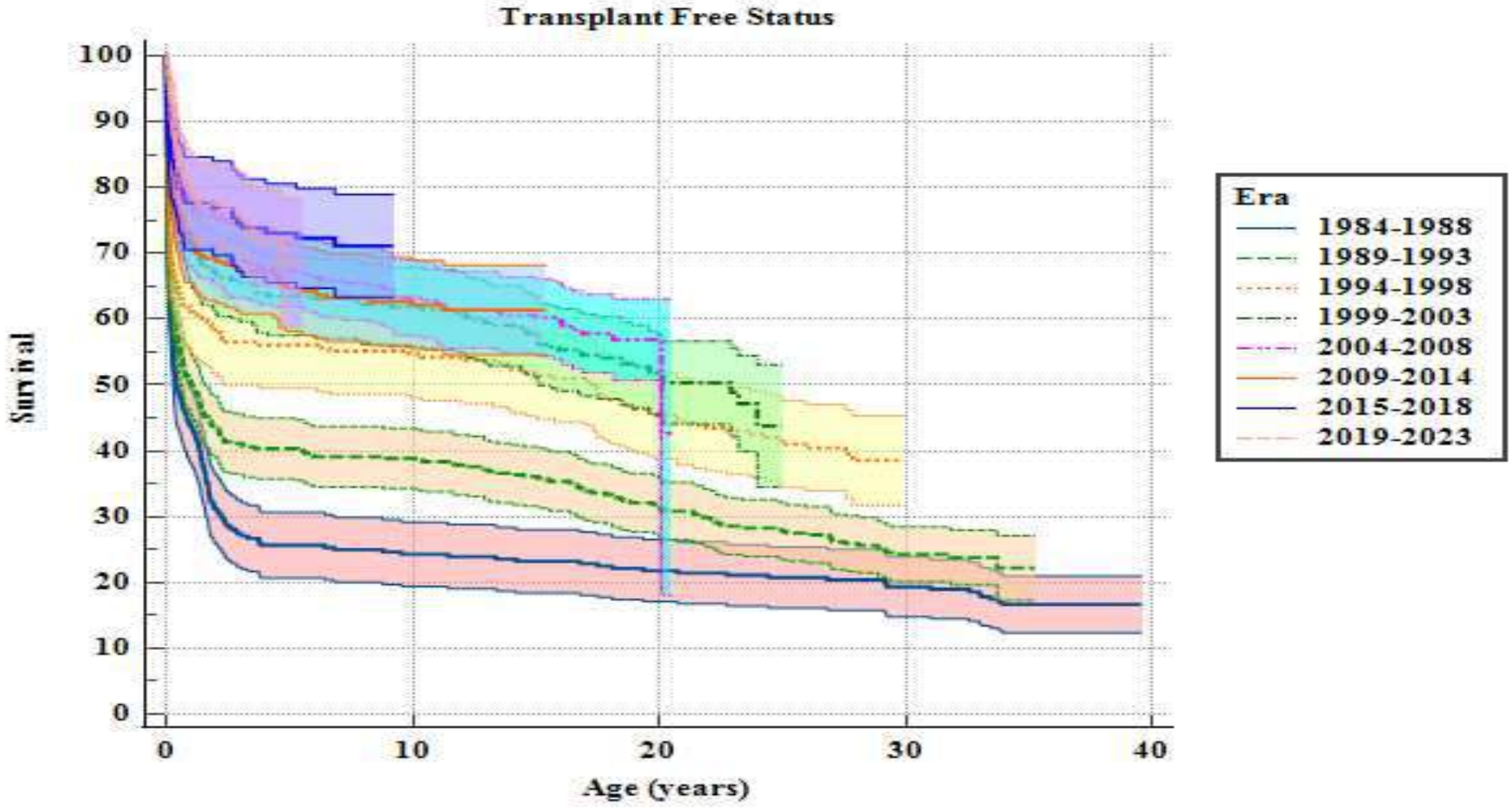



Transplant-free survival was 63.0% at 1 year of age, 51.7% at 10 years, 43.7% at 20 years, **and 31.0% at 35 years**.

**Independent Risk Factors**

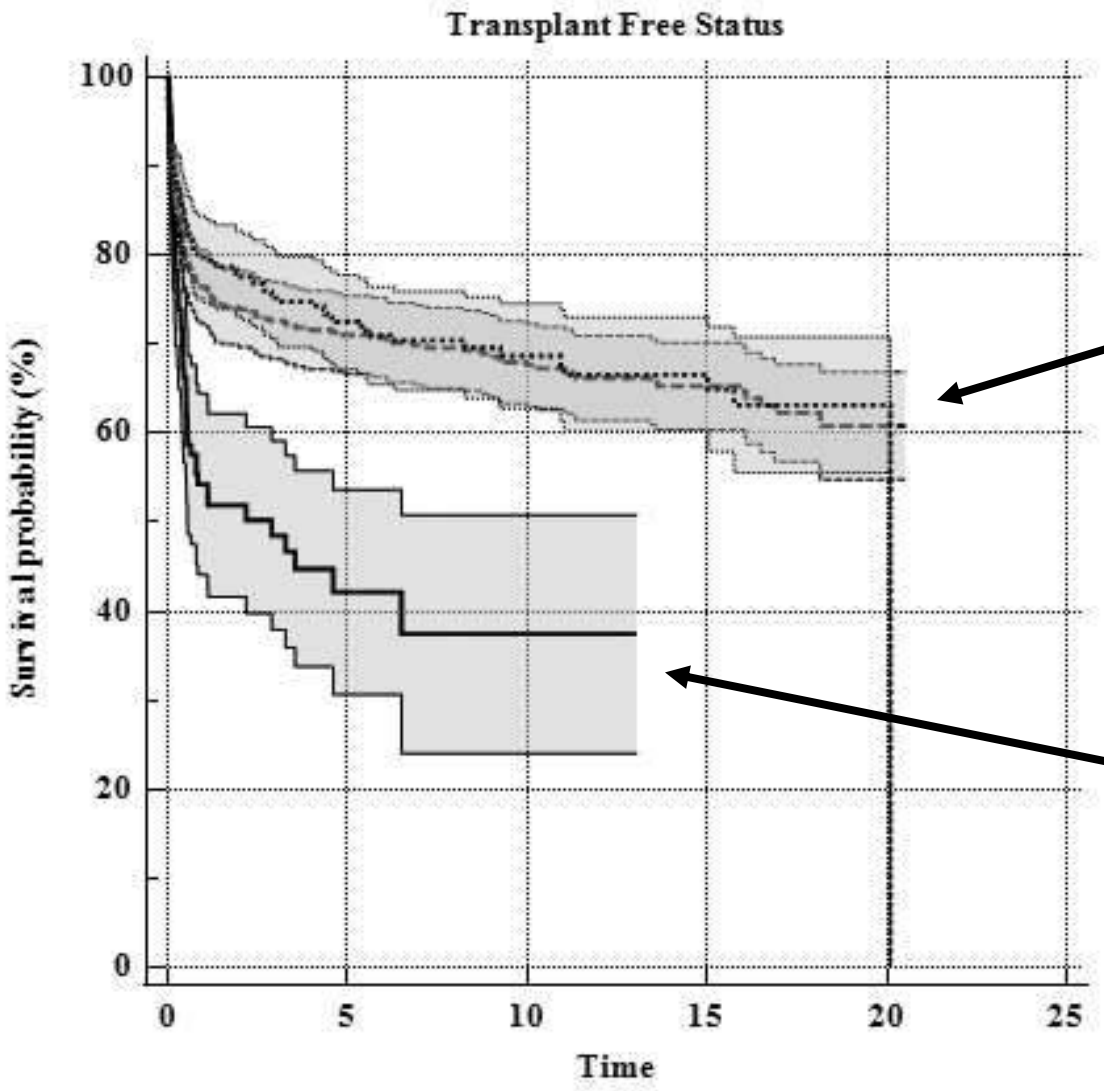
- Earlier Era
- Smaller Ascending Aorta
- Moderate to Severe AVVR
- Younger Gestational Age
- Genetic Anomaly
- Non-white Race

# Long-term Survival after Reconstructive Surgery for HLHS




Adjusted survival improved from1984 to 2003, but has subsequently plateaued.

# Long-term Survival after Reconstructive Surgery for HLHS




Survival was not different for Norwood with MBTTS compared to the Norwood with the RVPA

After adjusting for patient characteristics, survival for the Hybrid Procedure was worse compared to the Norwood, $p < 0.001$.

# Longitudinal Follow-Up of Children With HLHS and Association Between Norwood Shunt Type and Long-Term Outcomes: The SVR III Study

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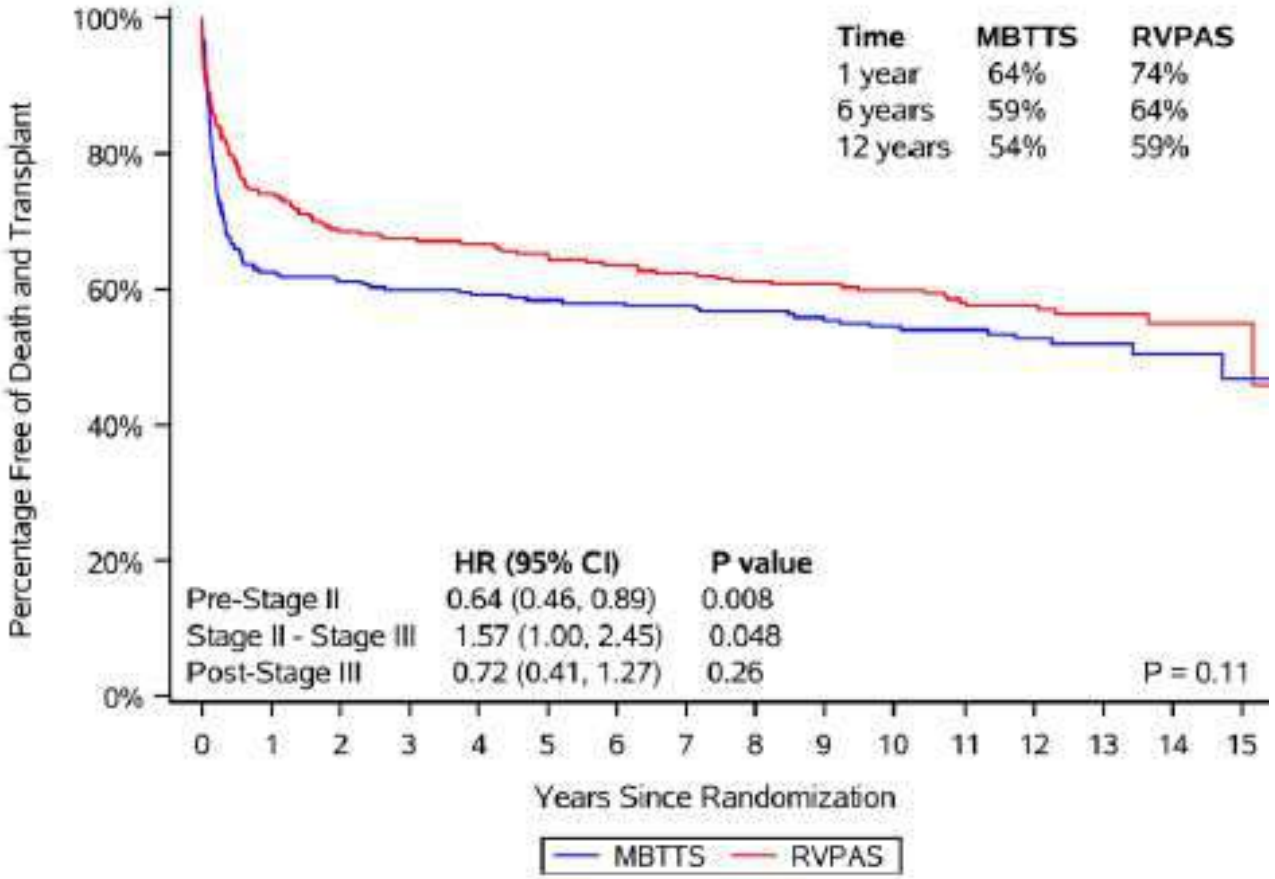
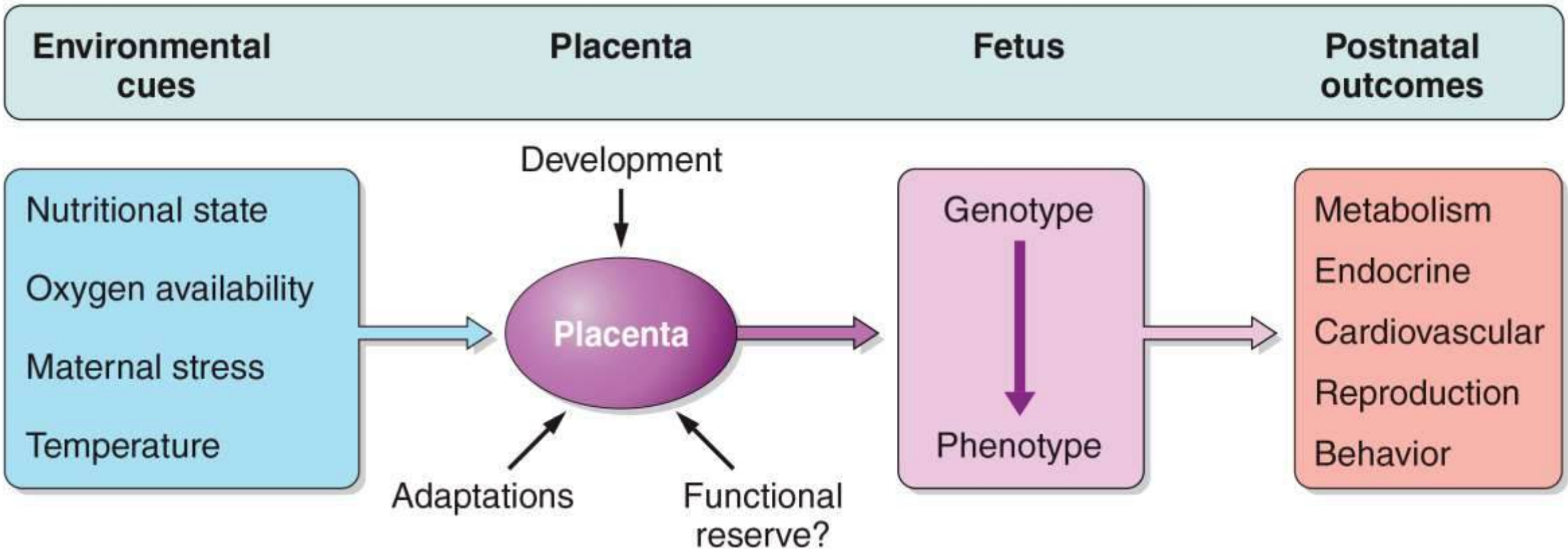



There is a critical need ***for further investment in innovative strategies to reduce the risks for morbidity and mortality.***

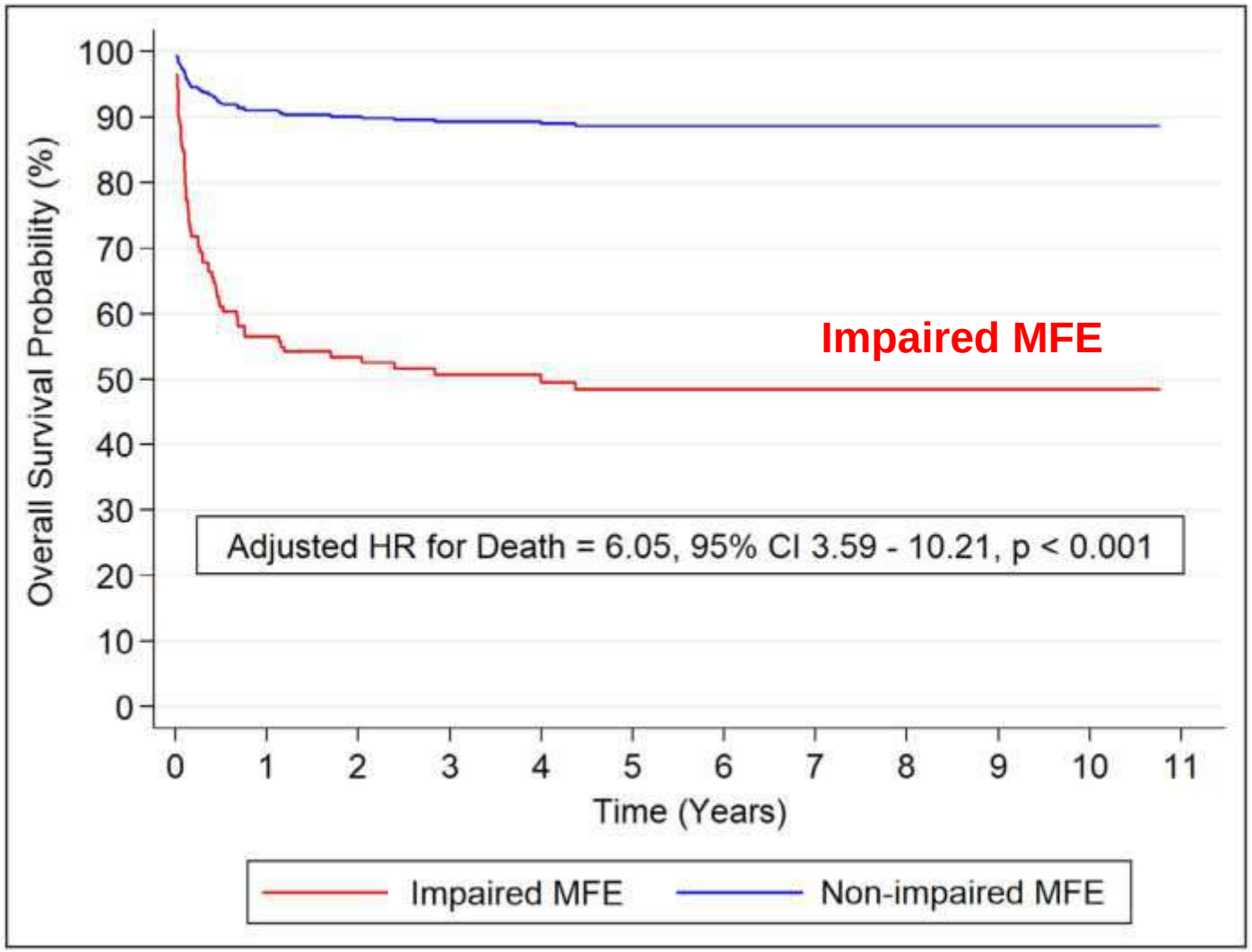
# PLACENTAL ORIGINS OF CHRONIC DISEASE

**Graham J. Burton, Abigail L. Fowden, and Kent L. Thornburg**



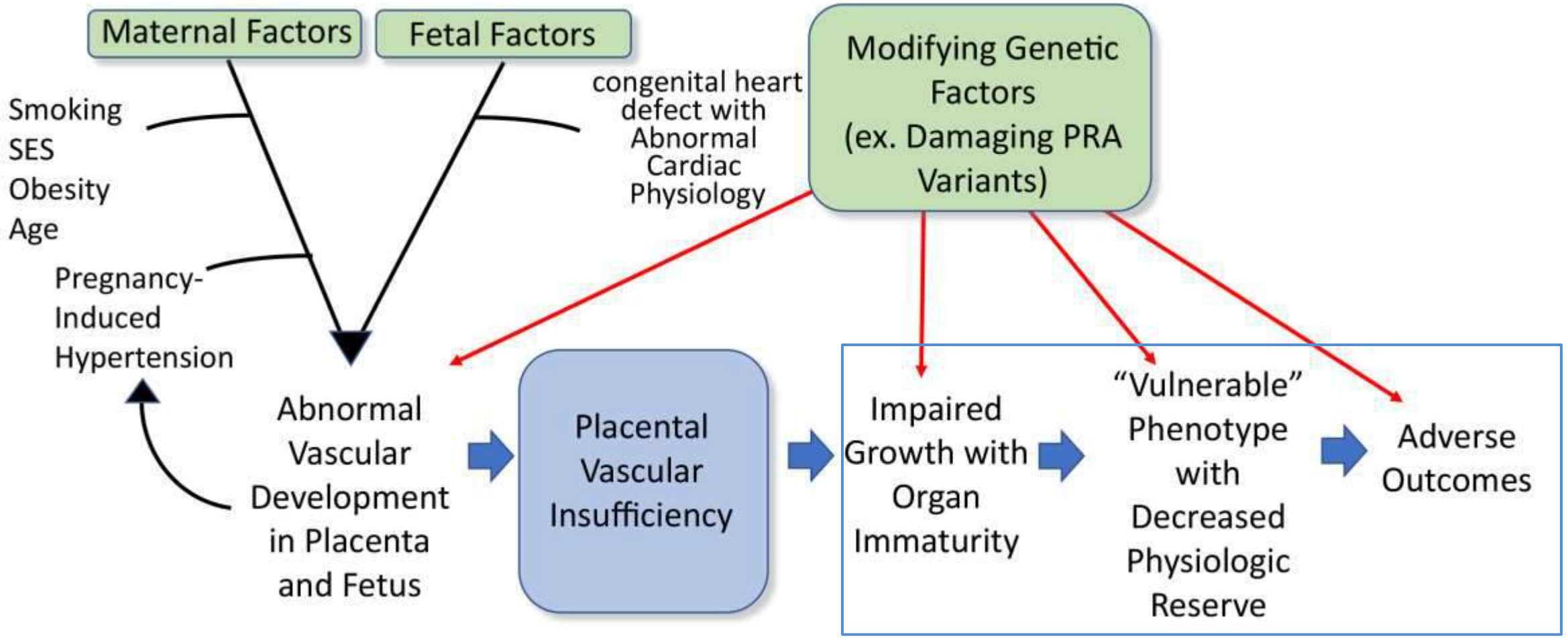
# Impact of Maternal–Fetal Environment on Mortality in Children With Single Ventricle Heart Disease

Jill J. Savla, MD, MSCE; Mary E. Putt, PhD, ScD; Jing Huang, PhD; Samuel Parry, MD; Julie S. Moldenhauer, MD; Samantha Reilly, BS; Olivia Yournan, BA; Jack Rychik, MD; Laura Mercer-Rosa, MD, MSCE; J. William Gaynor, MD; Steven M. Kawut, MD, MS



# Damaging Variants in Proangiogenic Genes Impair Growth in Fetuses with Cardiac Defects

Mark W. Russell, MD[1], Julie S. Moldenhauer, MD[2], Jack Rychik, MD[3], Nancy B. Burnham, RN, MSN, CRNP[4], Erin Zullo, BSN[4], Samuel I. Parry, MD[5], Rebecca A. Simmons, MD[6], Michal A. Elovitz, MD[5], Susan C. Nicolson, MD[7], Rebecca L. Linn, MD[8], Mark P. Johnson, MD[2], Sunkyung Yu, MS[1], Matthew G. Sampson, MD[9], Hakon Hakonarson, MD, PhD[10], and J. William Gaynor, MD[4]



# Progesterone and Brain Development

**Progesterone is a neurosteroid that is:**

1. essential in the establishment and maintenance of pregnancy,
2. neuroprotective and critical to brain development, and
3. utilized to prevent preterm birth.

# Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial

*Jane Elizabeth Norman, Neil Marlow, Claudia-Martina Messow, Andrew Shennan, Phillip R Bennett, Steven Thornton, Stephen C Robson, Alex McConnachie, Stavros Petrou, Neil J Sebire, Tina Lavender, Sonia Whyte, John Norrie, for the OPPTIMUM study group*

Double-blind, randomized, placebo-controlled trial of vaginal progesterone to prevent preterm birth.

Vaginal progesterone was not associated with a reduced risk of preterm birth.

| | Placebo group | Progesterone group | Unadjusted odds ratio (95% CI) or difference in means (95% CI) | p value (unadjusted) | Adjusted odds ratio (95% CI)* or difference in means (95% CI) | p value (adjusted*) |
|---|---|---|---|---|---|---|
| Fetal death or delivery <34 weeks of gestation | 108/597 (18%) | 96/600 (16%) | 0·86 (0·64 to 1·17) | 0·34 | 0·86 (0·61 to 1·22) | 0·67 |
| Neonatal morbidity or death | 60/587 (10%) | 39/589 (7%) | 0·62 (0·41 to 0·94) | 0·02 | 0·62 (0·38 to 1·03) | 0·072 |
| Cognitive composite score at 2 years†‡ | 97·7 (17·5) | 97·3 (17·9) | −0·48 (−2·77 to 1·81)§ | 0·68 | −0·48 (−2·77 to 1·81)§ | 0·68 |
| Components of the obstetric outcome | | | | | | |
| Fetal death | 7/597 (1%) | 8/600 (1%) | 1·14 (0·41 to 3·17) | 0·8 | .. | .. |
| Liveborn delivery before 34 weeks | 101/590 (17%) | 88/592 (15%) | 0·85 (0·62 to 1·15) | 0·29 | .. | .. |
| Components of the neonatal outcome | | | | | | |
| Neonatal death | 6/597 (1%) | 1/600 (<1%) | 0·17 (0·06 to 0·49) | 0·0009¶ | | .. |
| Bronchopulmonary dysplasia‖ | 18/574 (3%) | 17/580 (3%) | 0·94 (0·49 to 1·78) | 0·84 | .. | .. |
| Brain injury on ultrasound scan** | 34/574 (6%) | 18/584 (3%) | 0·50 (0·31 to 0·84) | 0·008 | .. | .. |

JAMA Network Open

Original Investigation | Pediatrics

# Progesterone for Neurodevelopment in Fetuses With Congenital Heart Defects
## A Randomized Clinical Trial

J. William Gaynor, MD; Julie S. Moldenhauer, MD; Erin E. Zullo, BSN; Nancy B. Burnham, RN, MSN, CRNP; Marsha Gerdes, PhD; Judy C. Bernbaum, MD; Jo Ann D'Agostino, DNP, CRNP; Rebecca L. Linn, MD; Brenna Klepczynski, BSN; Isabel Randazzo, BS; Gabrielle Gionet, MPH; Grace H. Choi, MS; Antoneta Karaj, MS; William W. Russell, MD; Elaine H. Zackai, MD; Mark P. Johnson, MD; Juliana S. Gebb, MD; Shelly Soni, MD; Suzanne E. DeBari, BS, RDMS, RVT; Anita L. Szwast, MD; Rebecca C. Ahrens-Nicklas, MD, PhD; Theodore G. Drivas, MD, PhD; Marin Jacobwitz, CRNP; Daniel J. Licht, MD; Arastoo Vossough, MD; Susan C. Nicolson, MD; Thomas L. Spray, MD; Jack Rychik, MD; Mary E. Putt, PhD, ScD

Phase II study to assess benefits of prenatal progesterone therapy on neurodevelopmental outcomes for fetuses with CHD and to inform the design of subsequent multi-center trials.

# Maternal Progesterone Study: *Study Design*

Baseline Echocardiogram

Baseline Brain MRI

Initiation of study drug

Vaginal Progesterone 8% gel (equivalent to 90 mg) or Placebo (vaginal moisturizer) BID

Interval Brain MRI

Pre- and Post-operative Brain MRI

Identification and Enrollment

Clinical Echocardiograms, Ultrasounds, and Physical Exams

Safety Evaluations q 1-4 weeks

Termination of Study Drug

ND Evaluation


24-28 weeks | 24-28 weeks | 34-36 weeks | 39 weeks | Birth | 18 Months

Gestational Age

Block Randomization: HLHS, TGA, OTHER

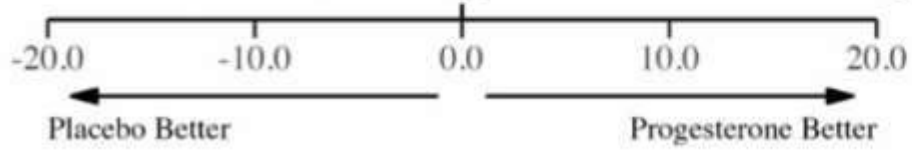
# Maternal Progesterone Study: *Neurodevelopment*

| BSID-III Score | Group Means[a] | | Treatment Effect | | | |
|---|---|---|---|---|---|---|
| | | | Pooled[b] | | Stratified[c] | |
| | Progesterone | Placebo | Mean (90% CI) | P-value | Mean (90% CI) | P-value |
| | Mean (SD) | | | | | |
| **Composite Scores** | | | | | | |
| **Motor** | 90.0(11.5) | 87.5(12.7) | 2.5(-1.9,6.9) | 0.34 | 2.7 (-1.6,7.1) | 0.30 |
| **Language** | 86.1(12.2) | 84.5(11.4) | 1.6(-4.5,7.8) | 0.66 | 1.7 (-4.4,7.9) | 0.64 |
| **Cognitive** | 92.4(15.1) | 91.2(18.9) | 1.2(-3.0,5.4) | 0.64 | 1.5 (-2.7,5.7) | 0.56 |

# Maternal Progesterone Study: *Neurodevelopment*

## Composite Motor Score

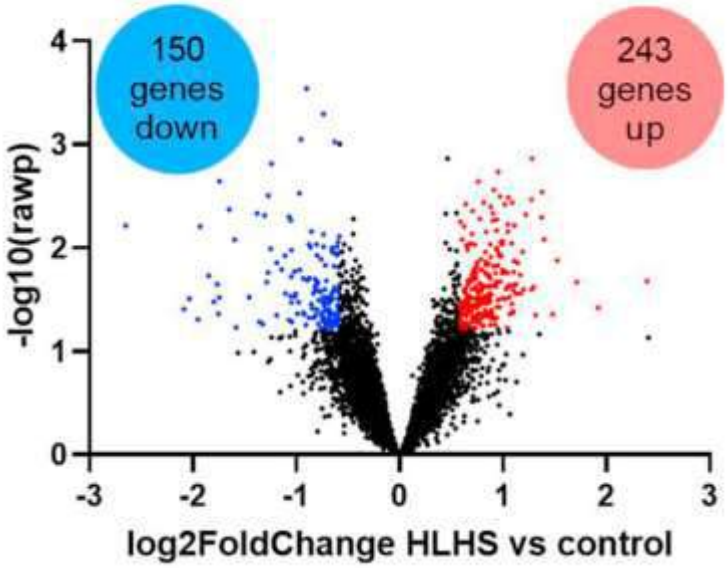
| Subgroup | Progesterone | Placebo | Estimate (90%CI) |
|---|---|---|---|
| Cardiac Diagnosis | | | |
| HLHS | 23 | 19 | 2.7 (-3.0 to 8.4) |
| Other | 6 | 6 | 17.3 (6.4 to 28.2) |
| TGA | 16 | 18 | -3.6 (-10.0 to 2.8) |
| Sex | | | |
| Female | 15 | 15 | 9.4 (2.5 to 16.3) |
| Male | 30 | 28 | -1.6 (-6.6 to 3.5) |
| Genetics | | | |
| Normal | 24 | 28 | 5.9 (0.6 to 11.1) |
| Suspect | 12 | 5 | -0.2 (-10.0 to 9.5) |
| Abnormal | 9 | 10 | -5.9 (-14.7 to 3.0) |
| Maternal-Fetal Environment | | | |
| None | 31 | 28 | 2.9 (-2.1 to 8.0) |
| Present | 14 | 15 | 0.8 (-6.6 to 8.2) |

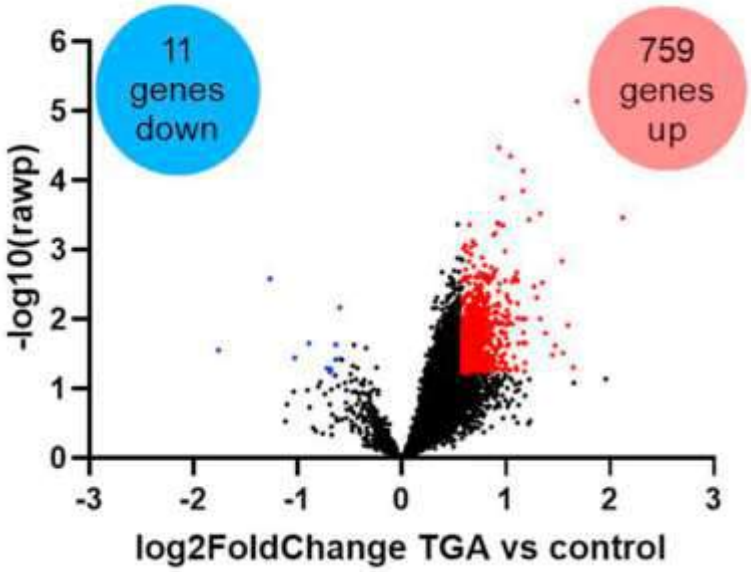


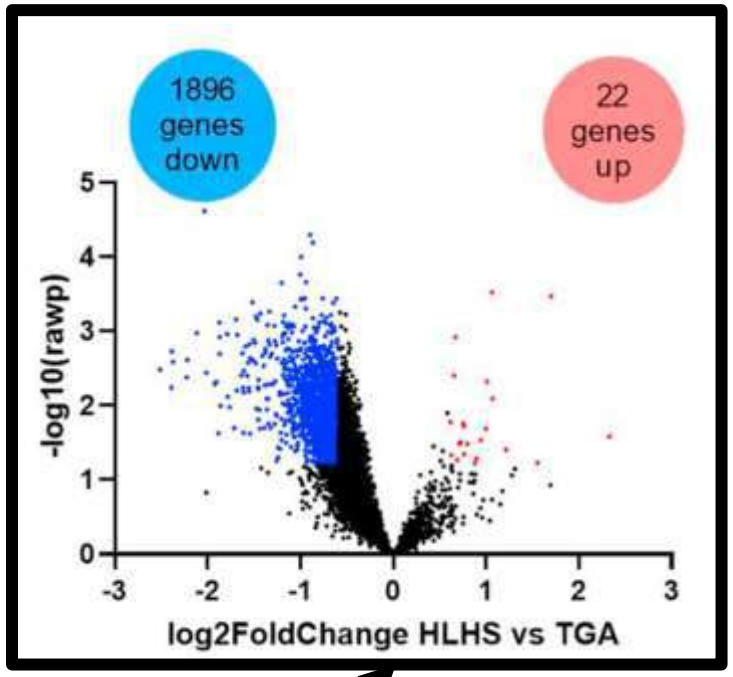
Abnormalities of placental development and function are associated with the different fetal growth patterns of hypoplastic left heart syndrome and transposition of the great arteries

Jennifer Courtney [a], Weston Troja [a], Kathryn J. Owens [a], Heather M. Brockway [d], Andrea C. Hinton [c], Robert B. Hinton [c], James F. Cnota [b], Helen N. Jones [d,*]

## Volcano Plots of Gene Expression from RNA-Sequencing




HLHS placentas had only 22 upregulated genes, but 1896 downregulated genes compared to TGA.

# Fetal sex and maternal pregnancy outcomes: a systematic review and meta-analysis

Zoe A. Broere-Brown[1,2], Maria C. Adank[1,2], Laura Benschop[1,2], Myrte Tielemans[3,4], Taulant Muka[3,5], Romy Gonçalves[1,2], Wichor M. Bramer[6], Josje D Schoufour[3,7], Trudy Voortman[3], Eric A. P. Steegers[1], Oscar H. Franco[3,5] and Sarah Schalekamp-Timmermans[1,2*]

…. the emerging concept of a sexual dimorphism in the maternal-fetal-placental interplay.

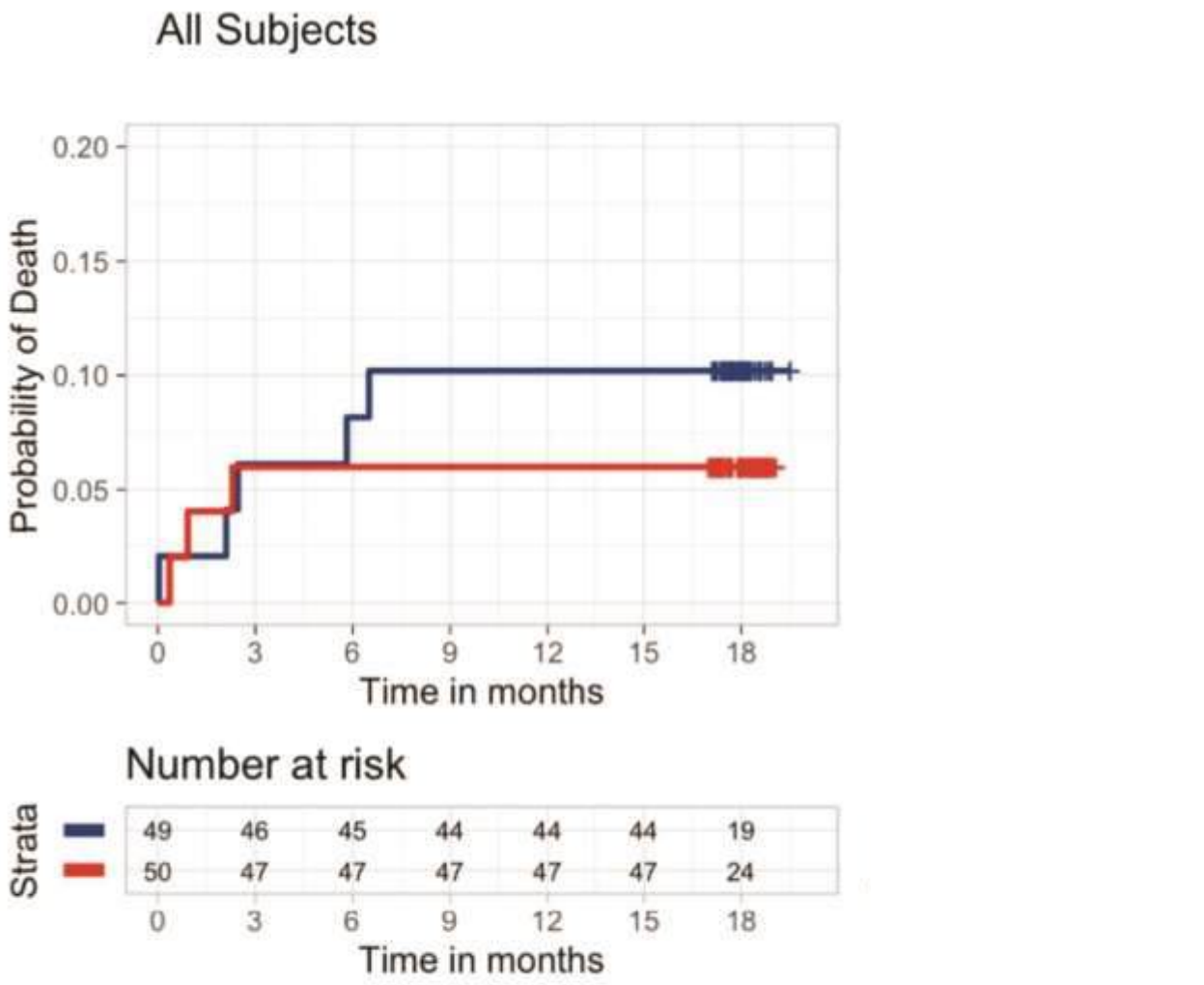
…. carrying a male fetus is accompanied with a higher cardiovascular and metabolic load for the mother resulting in maternal pregnancy complications and adverse health in later life.

# The Placenta's Role in Sexually Dimorphic Fetal Growth Strategies

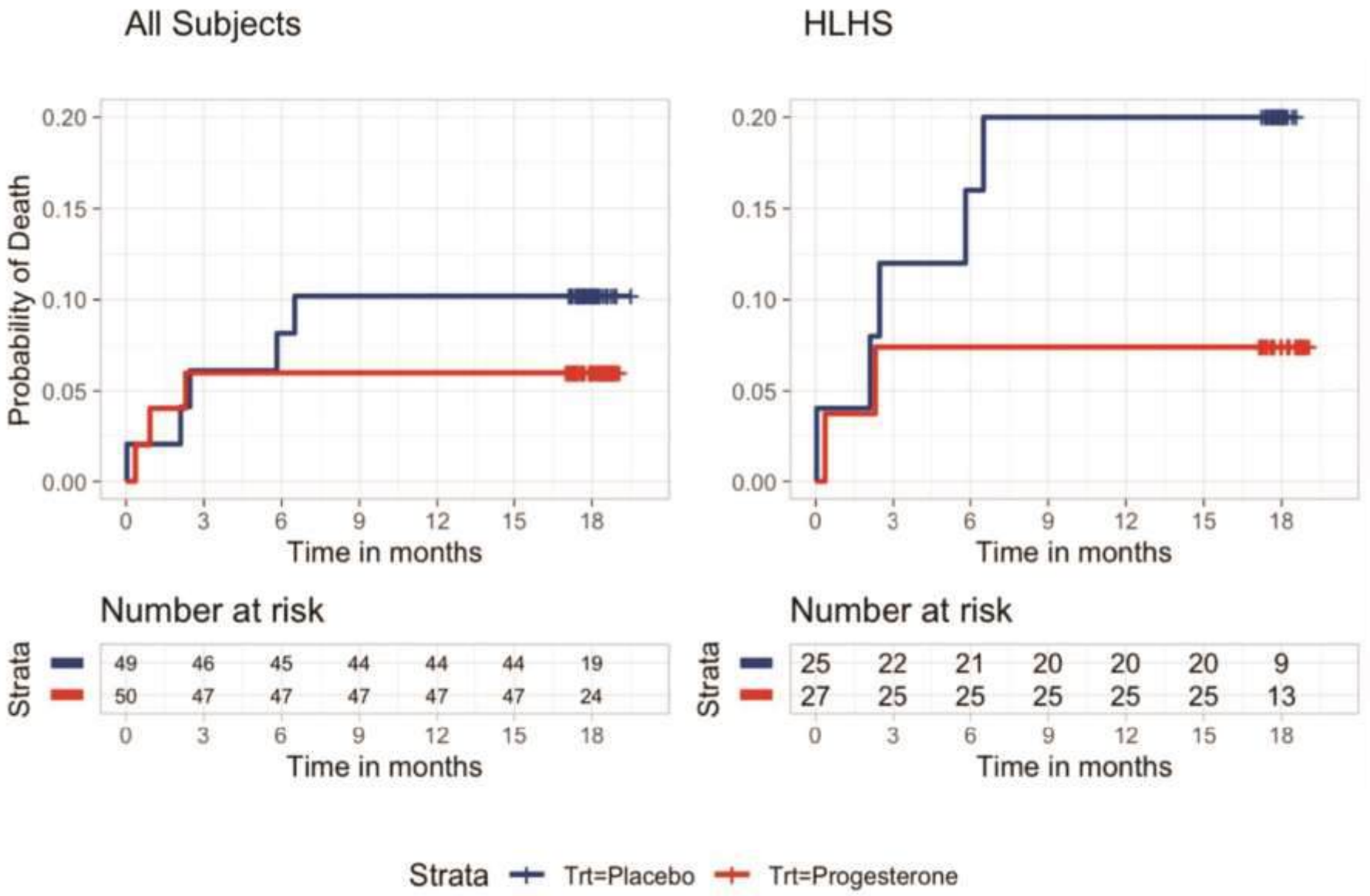
Julian K. Christians[1,2,3,4]

The sex chromosomes contribute to sex differences in placental gene expression, and fetal hormones may play a role later in development.

# Maternal Progesterone Study: *Impact on Mortality*



# Maternal Progesterone Study: *Impact on Mortality*



# Does Maternal Progesterone Reduce Morbidity and Improve Survival in Hypoplastic Left Heart Syndrome?

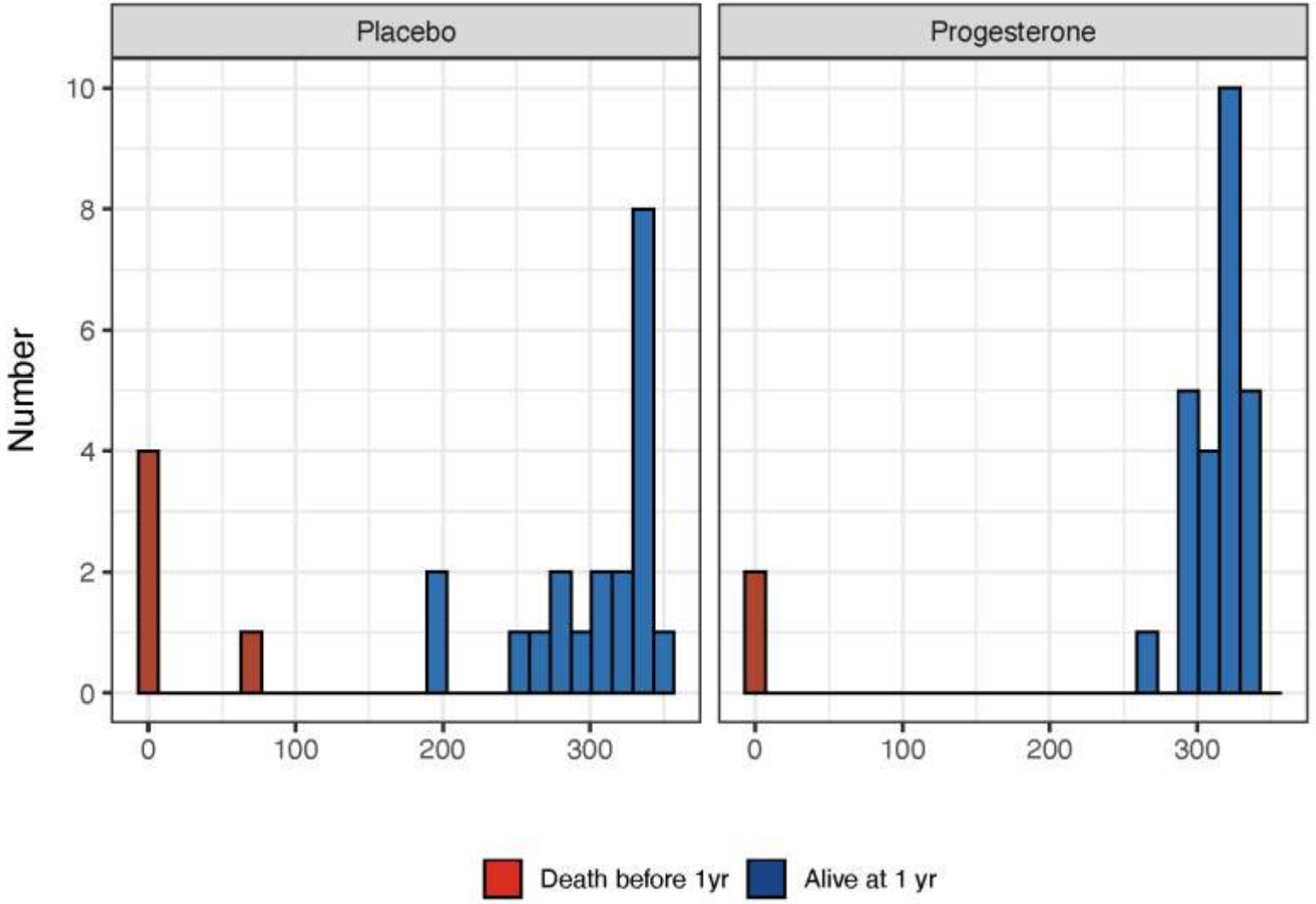
Secondary analysis to estimate the magnitude of the effect of progesterone treatment on morbidity and transplant-free survival for neonates with CHD.

**Outcomes:**

- Days alive and out of the hospital (DAOH in the first year of life)
- Transplant-free survival
- Placental weight and birthweight

**Impact of Maternal Progesterone on Morbidity and Survival in Hypoplastic Left Heart Syndrome**

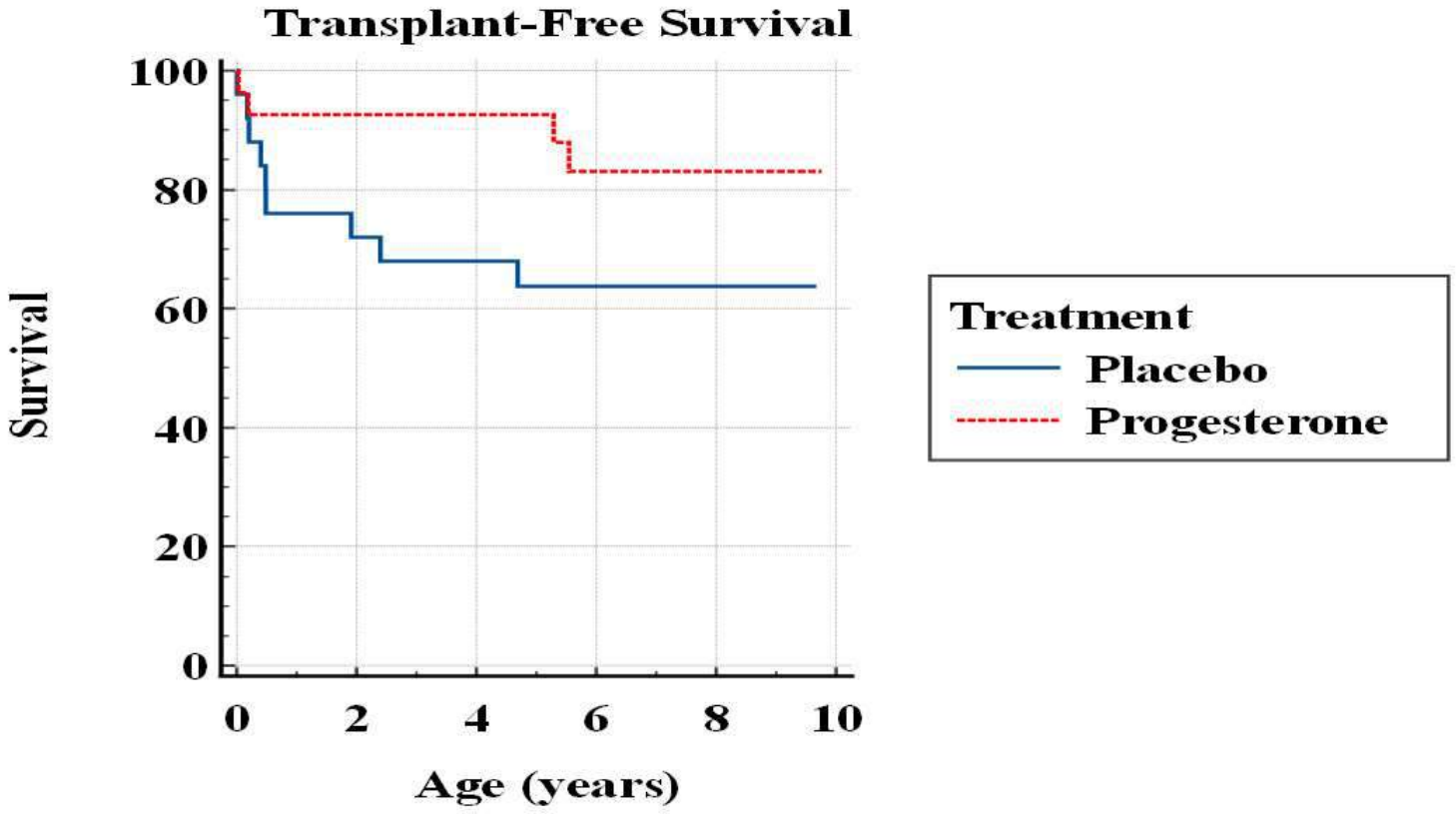
# Days Alive and Out of the Hospital (DAOH)




***Mean DAOH was 46 days longer for Progesterone*** (291 days) versus Placebo (245 days).

***Median DAOH (304 days) for Placebo was similar to a recent multi-institutional cohort of 304 days***, and was greater for Progesterone (315 days).

# Transplant-free Survival

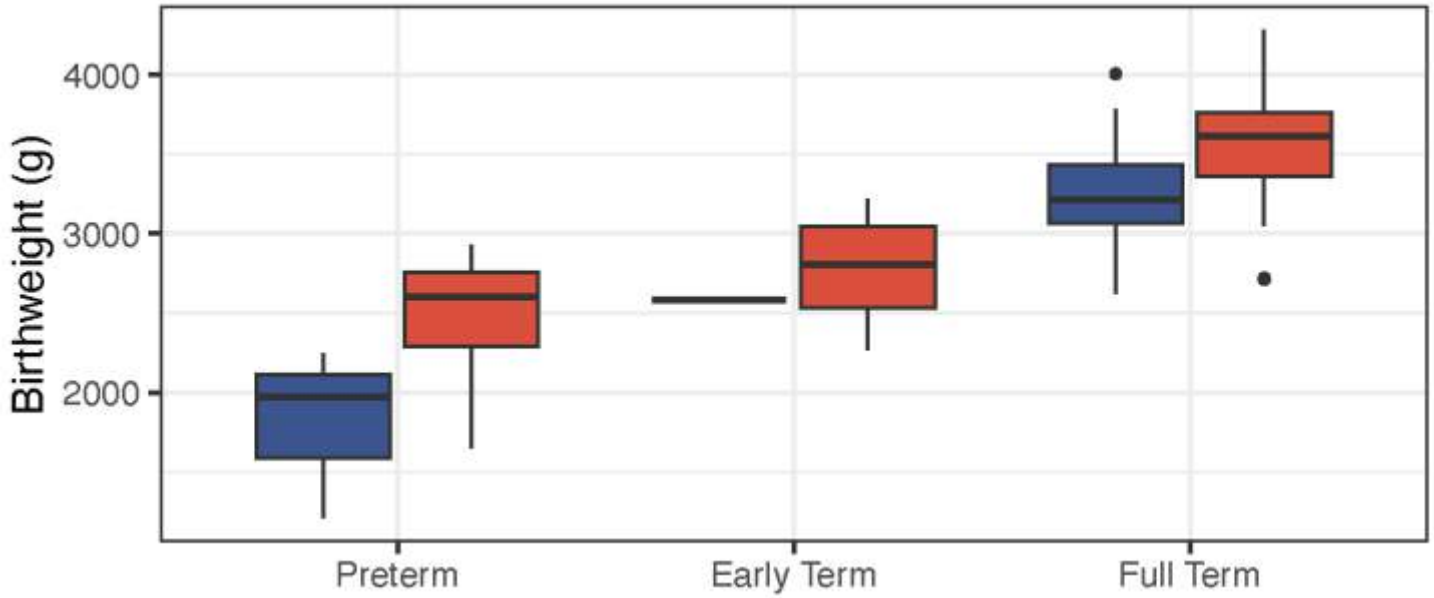



The risk of death or transplant was 0.36-fold smaller for Progesterone versus Placebo, P=.08 Log-rank Test).

***Transplant-free survival at 6 years was 83% for Progesterone versus 64% for Placebo***; which is similar to the 6-year survival reported by the SVR Trial.

**Impact of Maternal Progesterone on Morbidity and Survival in Hypoplastic Left Heart Syndrome**

# Birthweight




After adjusting for gestational age, birthweight (mean difference 337 gm., P=.005) was larger for infants in the Progesterone group, with no difference in placental weight suggesting greater placental efficiency with Progesterone.

Each 100 gm increase in birthweight was associated with an additional 5.4 DAOH, P=.05

# Impact of Maternal Progesterone on Morbidity and Survival in Hypoplastic Left Heart Syndrome

**In this small Phase II study:**

***DAOH was greater for Progesterone*** compared to Placebo.

***Transplant-free survival was greater for Progesterone*** compared to Placebo.

***Birthweight was greater for Progesterone*** compared to Placebo consistent with better placental efficiency.

***Larger birthweight was associated with increased DAOH***.

These findings suggest that Progesterone may improve outcomes by ***improving placental efficiency and fetal growth.***

A pivotal trial is needed to fully investigate the impact of progesterone treatment in HLHS.

# Aspiration or Illusion?
## *Improving Survival Outcomes for HLHS*