Laser therapy for Twin-Twin Transfusion Syndrome - Is it the end of the story?

Helena Gardiner, M.D.
Co-Director, Fetal Cardiology Program
Texas Fetal Center
Disclosure Statement

• I do not have relevant financial relationships with commercial interests related to the content of this presentation.
Normal variations in fetal size at birth have implications for health throughout life.
Learning Objectives

1. Explain the influence of the intrauterine environment on fetal vascular programming

2. Describe the influence of laser therapy on vascular development and peripheral micro-vascular behavior in monochorionic diamniotic (MCDA) twins

3. Counsel families concerning the long term effects of TTTS and the importance of screening for prevention of related conditions
Early Influences on Vascular Development

Cardio-placental rather than cardiopulmonary relationship
DOHaD: link between epidemiology and mechanisms

• Thrifty genotype
  Neel 1962: gene selection from hunter-gatherer ancestors

• Thrifty phenotype
  Hales and Barker 2001: adaptation to a nutritionally adverse environment

• Programming
  Hardwiring - rigid response to environment

• Life history and evolution

• Plasticity of response at critical windows leading to disruption or modulation of development

• Epigenetic regulation and stochasticity
Fetal Programming: first hypotheses

- Infant and stillbirth rates in siblings of those with Coronary Artery disease were twice as high as in whole population

- Past infant mortality correlated with areas showing current high levels of arteriosclerotic disease in Norway

- Higher blood pressure associated with growth restriction
Maternal constraint

Walton and Hammond, 1938

Limits ability of fetus to predict environment

• Competing interests – paternal influences to create the largest offspring and maternal interests to reduce size

• IGF-2 imprinted in mouse from paternal allele and receptor in placenta from maternal allele (Haig and Graham, 1991)

• IGF1 & insulin most important determinants of growth in species with long gestation - humans
Predictive adaptive responses

Meadow vole: maternal melanin determines coat thickness for life in its offspring, depending on season of birth

Prediction must be accurate!
Immediate adaptive responses

As the pool dries up the tadpole becomes a toad
early survival vs reduced adult fitness
But, MCDA twins are genetically identical....

What factors modify the genome?
Epigenetics

Transient environmental influences during development can permanently alter epigenetic gene regulation resulting in metabolic imprinting affecting disease susceptibility.

Mechanisms include CpG methylation, histone modifications, and autoregulatory DNA-binding proteins.

Epigenetic epidemiology provides a basis for future studies of early life exposures, epigenetic mechanisms, and adult disease.
Epigenetics in action!
In addition to genetic and epigenetic inheritance, stochasticity (unpredictability) affects the developmental establishment of epigenetic regulation.

Environmental influences on epigenetics are likely to be most important during prenatal and early postnatal development.

Cumulative errors in maintenance of epigenetic information will contribute to inter-individual epigenetic variation with age.

Epigenetic Epidemiology of the Developmental Origins Hypothesis
Monochorionic twins are special
Is the Programming hypothesis untrue for twins?

Epidemiological studies have confounders:

- Maternal recall in small studies
- Cross-over of pre and postnatal data
- Chorionicity unknown

Price, 1950

In-utero environment is more severe in MZ twins and may be more discordant than for DZ twins, thus undermining any genetic effects
How does the “Barker Hypothesis” apply to twins?

• Low ponderal index – “thin & long”
• Twins are 0.8-0.9 kg lighter than singletons
• Born earlier and exhibit catch-up growth
Early Influences on Vascular Development

Shared circulation in all MCDA allows between-twin transfer of substances.
Hostile intrauterine environment
Haemodynamics in TTTS

**Recipient**
- Chronic volume loading and increased impedance
- Raised endothelin, ANP and reports of neonatal hypertension

**Donor**
- Hypovolaemia – increased renin production
- Increased distal impedance
- Chronic vasoconstriction
- Growth restriction
CVS sequelae of TTTS - adaptive or disruptive?
Prenatal cardiovascular manifestations in the twin-to-twin transfusion syndrome recipients and the impact of therapeutic amnioreduction

Catherine Barrea, MD, a Fawaz Alkazaleh, MD, b Greg Ryan, MB, b Brian W. McCrindle, MD, a Anita Roberts, BSc, a Jean-Luc Bigras, MD, a Jon Barrett, MD, c Gareth P. Seaward, MB, b Jeffrey F. Smallhorn, MB, BS, a Lisa K. Hornberger, MD a,*


Conclusion: In twin-to-twin transfusion syndrome, the recipient twin has progressive biventricular hypertrophy with predominant right ventricular systolic and biventricular diastolic dysfunction. Despite amnioreduction, the cardiovascular disease persists and even progresses in many recipient twins.
If nothing seems wrong, is everything normal?

FETAL VASCULAR PROGRAMMING
TWIN-TO-TWIN TRANSFUSION SYNDROME
... A FOLLOW UP STUDY

University Clinic, Hamburg-Eppendorf, Germany

Queen Charlotte’s and Chelsea Hospital, London
Hypotheses

• Differences in fetal haemodynamics programme later arterial behaviour
• This may be reversed by early resolution of haemodynamic imbalance i.e. Laser therapy

Aims

• Compare the arterial stiffness (PWV) in surviving twin pairs with and without TTTS
• Compare PWV in those treated with amnioreduction and laser
Patients, n=100 twins and methods

- 14 pairs of TTTS managed by serial amnioreduction
- 13 pairs of TTTS treated by laser (median age of 22 weeks)
- 12 pairs of MCDA without TTTS
- 11 pairs of DCDA

All MCDA had undergone serial prenatal Doppler studies

- Birth weight, gestation age
- Corrected age at examination
- BP of right upper limb (by Dinamap)
- Pulse Wave Velocity using a photoplethysmographic technique
Infrared diode & photo-transistor

Reflected portion of infrared varies with diameter change of artery.

Signal Level

Upstream

Downstream

Flow

Artery

Muscle
Pulse Wave Velocity

Transit time determined from time delay between the foot of the brachial and radial pulse waves

PWV = distance between 2 probes / transit time
Similar measurements between the 4 groups

- Median age 11 months
- No difference in postnatal age at scan
- No differences in blood pressure
- No intra-pair differences in cord Haemoglobin
- No differences in birth weight Z-score of lighter twin in the TTTS groups i.e. similarly growth restricted

Differences in fetal haemodynamics programme later arterial behaviour
This may be reversed by early resolution of haemodynamic imbalance

Results: PWV difference heavy-light, p=0.01, contrast -1.99, 95% CI [-3.52 to -0.45]

Take-home message: vascular programming occurs in MC twins
It is altered by laser to resemble that seen in DC twins
Study part one: Summary of PWV results

• PWV is increased in infancy in the donor twin in TTTS pairs of survivors treated by amnioreduction

• Between-twin discordancy increases with duration of disease

• Adaptive vascular remodelling may ensure survival but may prejudice later cardiovascular health

• Laser intervention seems to reverse or prevent these changes
Vascular programming: possible mechanisms

• Increased renin gene and protein expression in donor kidneys with virtually absent expression in the recipient kidney

• Increased angiotensin II activity in the recipient fetus.

• Shorter duration of disease in the laser treated TTTS group (median age of 22 weeks)

• Critical period for vascular programming

• Hypothesis that third trimester abnormalities of elastin deposition may be responsible for reduced arterial distensibility
What of later outcomes for MCDA twins with TTTS?

Window of developmental plasticity reverses the prediction that haemodynamic factors will permanently alter arterial stiffness
Re-studied twins ~ 11 years old

- PWV - measure arterial stiffness in large arteries
- Blood pressure
- Microcirculation in the hand at rest (Flux), in response to occlusion of the limb and local heating using laser Doppler flow
Why study the microcirculation?

- Microcirculation is affected by reduced nutrition
- Flow mediated dilatation (FMD) is affected by low birth weight
- Suggests peripheral vascular beds and their control is altered by poor intrauterine nutrition

MCDA twins show discordant growth - often due to unequal placental share

PWV and Blood Pressure

- Similar within-pair differences in arterial stiffness remained at 11 years, suggesting a long term benefit of laser Rx
- Diastolic BP lower in all monochorionic twins
- Systolic BP lower in all TTTS compared to DCDA

Mixed Models analysis: included current blood pressure and growth since first study and any effects of the first measurements
Results: Microcirculation

Resting flux:

- All monochorionic twins had increased resting flow in the microcirculation compared to DCDA twins
- Heavier or recipient twins > donor or lighter MCDA

Post-occlusion (PORH) response (indicator of endothelial function)

- DCDA showed increased response vs TTTS-amnio + MCDA
- DCDA and laser treated MCDA showed similar responses
- Time to peak response: heavier /recipient > donor/lighter

Response to skin heating

- No apparent differences between groups
Summary of Results

- PWV is lower in TTTS groups than MCDA controls
- Diastolic blood pressure is lower in all Mono than DCDA twins
- Systolic BP is lower in TTTS groups than DCDA
- Resting capillary flow (microcirculation) is greater in all Mono twins and in the recipient/heavier twin
- PORH is higher, suggesting better endothelial function in DCDA than TTTS-amnio and MCDA controls
- PORH is similar in DCDA and TTTS-laser
- Although within-pair group patterns of arterial stiffness are similar to first study, mixed models = NS
Interpretation

• Monochorionicity and inter-twin fetal blood transfusion may alter vascular development of the circulation resulting in lower peripheral resistance as evidenced by greater arterial compliance, lower blood pressure and increased resting skin blood flow.

• We do not know whether there are more capillary vessels, or whether they are more dilated at rest

• Endothelial function may be reduced in uncomplicated monochorionic pregnancies and TTTS treated by amnioreduction
Interpretation

• Ex-Donor and recipient twins show the same patterns of arterial stiffness as in early childhood, but these are not significant because of the effects of BP and growth in the model

• However all heavier –born twins of a pair showed more baseline skin perfusion and slower response to occlusion

• Where inter-group differences exist, TTTS-laser children are similar to DCDA controls

• This suggests separation of the placental anastomoses to cure TTTS alters vascular programming

Is TTTS a cardiovascular life sentence?

Not if you have a good laser service!