The ‘fetus as a patient’: the role of fetal therapy: is this as good as it gets?

Mark. D Kilby.
Centre for Women’s & Children's Health, University of Birmingham & Fetal Medicine Centre, Birmingham Women’s Foundation Trust.
Sims Black Lecturer, 2015.

Visualization of the fetus.

Leonardo's study of a fetus in the womb (c. 1510) Royal Library, Windsor Castle.

Lennart Nilsson. “A Child is born”.

Visualisation of the fetus: the development of ultrasound

Ian Donald CBE MBE DSc FRCOG, FRCS, FRCR.
Regius Professor, University of Glasgow (1958).

2D ultrasound to image the ‘fetus’

Fetus as a ‘patient’

- Visualisation of the ‘second patient’: Ultrasound
- Primarily as a consequence of ‘technological advance.’
- The subspecialty of Fetal Medicine allowing a wide array of diagnostic & therapeutic interventions

(ACOG,1988; AAP,1989)
**Fetal therapy**

- The impetus for fetal treatment came from obstetricians, pediatricians & surgeons frustrated by disease processes already untreatable at (still)birth.
- Better visualization of the fetus led to the establishment of ‘perinatologists’.
- Techniques for indirect and direct (endoscopic) visualization of the fetus made interventions possible.
- Establishment of multi-disciplinary teams.
- Understanding of disease & ‘developmental’ pathogenesis: but this has lagged behind visualization.

**Red cell alloimunisation**

**Fetal IUTs: Outcome**

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Over an 8-year period, 1997-2004, 221 in-utero transfusions were performed for fetal anemia (Somerset et al. Fetal Diagn Ther. 2006;21(1):272-6).

| Intrahepatic vein puncture | Placental cord root |

**Twin-to-twin transfusion syndrome**

This complicates up to 1 in 5 DA / MC pregnancies and accounts for at least 40% of all twin perinatal mortality.
Unidirectional arterio-venous anastomoses with different calibre

Fetoscopic laser ablation

Unidirectional arterio-venous anastomoses with different calibre

Fetoscopic laser ablation

Survivors in each pregnancy

Fetoscopic laser ablation

Percentage of pregnancies

Overall survival

Recipient survival

Donor survival

Overall neurological Morbidity

Recipient survival

Overall survival

Recipient survival

Donor survival

Systematic Review of the literature.

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**Fetoscopic laser ablation:**

*Unidirectional arterio-venous anastomoses with different calibre.*

**Fetoscopic laser ablation:**

*Survivors in each pregnancy.*

**Systematic Review of the literature.**

*Overall survival vs Serial amnioreduction:*

- Necker: 1.49 (0.31, 2.04)
- Quintero: 1.32 (0.85, 2.03)
- Senat: 2.07 (1.30, 3.29)

*Overall neurological Morbidity:*

- Necker: 1.49 (0.31, 2.04)
- Quintero: 1.32 (0.85, 2.03)
- Senat: 2.07 (1.30, 3.29)
Fetal structural malformations

- Many congenital, structural anomalies (5% of pregnancies) are associated with increased risk of perinatal loss & morbidity.
- Paediatric interest in altering the rate of progression of disease by surgical means.
- Understanding of the pathogenesis is poor and incomplete.
- Enthusiasm for fetal surgery between 1970-2002, especially in the USA.

Potential for fetal surgery.

- Modification of progression of in-utero ‘structural’ malformations is controversial.
- Maternal morbidity (and theoretically mortality)
- Potential fetal anomalies potentially managed by ‘fetal surgical’ intervention:
  - Neural tube anomaly correction.
  - Congenital diaphragmatic hernia.
  - Lower urinary tract obstruction (LUTO).
  - Large fetal tumors.
  - Diseases with placental anomaly (i.e. TTTS).

The role of in-utero surgery?

- Human ‘open surgery’ (Harrison et al, 1993)
  - Hysterotomy at 23-27 wk.
  - Maternal HDU care
  - Aggressive tocolysis
  - Fetal surgery (i.e. reduction & repair / abdominoplasty).

- San Francisco experience (1991-1993)
  - Still only variable survival (i.e. in CDH approximately 30%)
  - Considerable maternal morbidity (i.e. haemorrhage / infection)
  - Amniorrhesis (20%) & high risk of pre-term labor.
  - Fetal distress and associated fetal cardiovascular changes associated with liver return to abdomen.

In-utero surgery for myelomeningocele (1)

- Prenatal diagnosis early in gestation.
- Progressive neurologic impairment.
- Poor prognosis (certainly high morbidity)
- Animal models indicate that open operation (split skin graft held in place by fibrin glue) early in-utero (<24 weeks) leads to:
  - prevent/reverse neurologic deficit.
  - preservation of spinal cord cytoarchitecture. (Copeland et al, 1993; Meuliet et al, 1995)

In-utero surgery for myelomeningocele (2)

- Multicentre RCT (CHOP, San Francisco & Vanderbilt University Medical Center).
- Prior to 25th week & delivery at 38 weeks by C/S.

At 30 months:
- Increased rates of children ‘walking independently’ (42% prenatal vs. 21% postnatal).
- Lower requirement for postnatal ventriculo-peritoneal shunt placement.
- Higher risks of PPROM, oligohydramnios & preterm birth in prenatal surgery.
- 33% of women had ‘scar thinning or dehiscence’.


Open surgery for Spina Bifida.

Congenital diaphragmatic hernia

- Why does CDH carry a poor prognosis?
- What factors affect prognosis?
- Are there any ‘therapy’ to improve prognosis?

“Despite antenatal diagnosis, more than 80% of babies with CDH on ultrasound will die”
(Harrison, 1990)
West Midlands Congenital Anomaly Register


Prediction of pulmonary hypoplasia

Predictive of PH in CDH if:

a) Liver in the fetal chest.
b) LHR<1 (More recently the O/E ratio has proven to be more sensitive)

FETO for improving outcome in CDH

Fetoscopic laryngoscopy  Fetal ‘transient tracheal occlusion’
Newsworthy

“Identical Twins Survive Cutting-Edge Laser Surgery”

Critical appraisal of evidence for Fetal Therapy

- Evaluation of evidence using systematic reviews of cohort studies.
- Robust evaluation of short & (importantly) long term outcomes.
- International collaboration
- RCTs / comparative cohort studies
- Robust evaluation of ‘techniques’.
- Institutional & personal governance
Fetal lower urinary tract obstruction (LUTO)

- 30% of renal tract anomalies detected at autopsy (Brand et al 1994)
- Heterogenous number of pathologies:
  - Posterior urethral valves (PUV) 64%: (Commonest, usually males)
  - Urethral atresia 39%
  - Cloacal plate anomalies, including megacystis microcolon syndrome
  - ‘Prune Belly syndrome’ 4%


Vesico-amniotic shunting vs. Conservative management in LUTO

Kaplan-Meier survival: PLUTO

- RCT data trend towards improved perinatal survival with shunting but with an increased risk of pregnancy loss. In RCT, the 'as treated analysis' demonstrated that VAS improved perinatal survival to 60% as compared to no intervention (19%; p=0.03).
- At 2 years of age only 2 babies of 7 (28%) survivors post-VAS were alive with no renal impairment. Morris et al, 2013. Lancet. In Press

National initiatives for ‘standards’ in Medicine

“Standardised Mortality Rates”

Sir Bruce Keogh, the medical director of NHS England, said the figures were among a "constellation of reasons" to suspend operations.

Leeds Children’s Hospital Heart Surgery
What of Fetal Medicine and Therapy?

"To set CQUINs (standards) in Fetal Medicine to which remuneration is linked"

Is this a problem & is it applicable to Fetal Medicine?

West Midlands Fetal Medicine Centre
Annual Report: since 1997

- Documentation of staff and resource.
- Documentation of workload in all areas (i.e. no: ultrasounds, amniocentesis, CVS and therapeutic procedures).
- Documentation of overall outcomes (i.e. overall procedure related losses at amniocentesis/CVS and therapy outcomes).
- Outcomes are not individuals but institutional.
- Part of Regional CQUINS.
- Research and Development Strategy

Fetal intravascular transfusion

Intrahepatic vein puncture  Placental cord root

Safe & low risk of vessel leak.  Ease of access/risk of ‘tamponade’

Superior & safe results by transfusion via IHV. Fetal Diagn Ther. 2006;21(3):272-6

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Recent national audit (BMFMS / BHS, 2013):
- Not all centres publish outcomes in public domain.
- Many Fetal Medicine units <20 IUTs per 5 yrs
- Some centres <5 IUTs per annum.
Fetoscopic laser ablation

Changing Survival rates as number of cases increases

Evaluation of refined techniques

RCT Selective ablation vs. “Solomon technique”

Logistic regression

Outcomes - number of procedures

Outcome for FLC for TTTS
**Cumulative summation test for learning curve**


- Centre-based learning: 76 cases to reach at least \( \geq 1 \) in 85% FLC.
- Continuing cumulative assessment.

_Biau DJ, Morris RK, Kilby MD, 2013._

**Comparison of operator (\& centre) competency**

Fetoscopic laser ablation (2004-2007). First 199 cases

Tolerance 1 or 2 fetal survivor(s) in 85% of procedures.

_Biau DJ, Morris RK, Kilby MD, 2013._

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**Conclusions**

- Better visualisation of the fetus by ultrasound and directly has allowed better forms of therapy to modify fetal pathologies.
- Improved understanding of pathogenesis is important for success as noted by the treatment of Rhesus disease by in-utero transfusion & laser for severe TTTS.
- New therapies are limited and critical appraisal of evidence for their introduction is important for both improvement of short and long term outcomes.
- Methods for improved techniques need robust evaluation.
- Need for a debate on how many centres should be performing these ‘relatively rare’ techniques and centre-based (individualised) outcome data.

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_Sims Black Lecturer, 2015_
Sims Black Lectureship,
Buenos Aires, 2015