Invasive Fetal Therapy

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Examples of Invasive Fetal Therapy

- Cordocentesis / Intrauterine Transfusion
- Fetal surgery
- Treatment of Twin-Twin Transfusion
- Stem cell therapy
- Gene therapy

Surgical Fetal Therapy

- The natural history and pathophysiology of the disease is well understood
- The prenatal diagnosis is accurate, capable of excluding other anomalies, and able to predict which fetuses have a sufficiently bad prognosis to justify in utero intervention
- In utero correction is shown to be efficacious in animal models
- Maternal risk is proved to be acceptably low

Cordocentesis and IUT - History

- 1963 - First intraperitoneal transfusion (Liley)
- 1974 - Fetoscopy to obtain fetal samples (Hobbins, et al)
- 1981 - Fetoscopic transfusion (Rodeck, et al)
- 1982 - First ultrasound guided IUT (Bang, Bock & Troll)
- 1983 - First large study of IUT - 66 cases (Daffos, et al)

Most Common Indications for Cordocentesis

- Genetic analysis 38%
- Alloimmunization 23%
- Infection 10%
- Nonimmune Hydrops 7%

(Hudkins, 1961)

Hemolytic Disease/Alloimmunization

- Most commonly due to Rh blood system
- Complex system involving several antigens
- Presence of D -> Rh positive
- Absence of D (called ‘d’) -> Rh negative
- Overall, 15-16% Rh - in the US
- Rare in non-Caucasians
- ABO incompatibility is somewhat protective

Rh Immunization - Causes

- Transplacental hemorrhage - delivery, amniocentesis, cordocentesis, abortion, trauma
- Becoming less common since introduction of Rh immune globulin in North America in 1968
- Blood transfusion - rare cause today due to blood typing for Rh

Rh Immunization - Effect on Fetus

- Maternal IgG anti-D causes fetal RBC destruction
- Fetal anemia
- Extramedullary hematopoiesis leads to hepatomegaly
- Fetal hydrops
- Fetal death
Rh Immunization - Maternal Immune Response

- Primary response is slow and is mostly IgM, which does not cross the placenta
- Secondary response is primarily IgG, which DOES cross the placenta
- Secondary response requires only low dose
Diagnosis of Rh Immunization

- Blood type of mother determined at first prenatal visit
- If Rh -, evaluate father of baby
- If anti-D is present, titer is important
- Must know ‘critical titer’ for specific lab/institution
- At JCMC, critical titer is 16
- If less than critical titer, needs to be followed
- Maternal history is important - previous infant with hemolytic disease, hydrops

The Liley Curve

- Described in 1961, gestational ages 27-41 weeks
- In normal amniotic fluid, the spectral absorption curve is linear from 365-550 nm (logarithmic curve)
- Bilirubin peaks at 450 nm
- The Δ OD 450 represents the difference between actual and expected
- Modified curve developed to extend to earlier gestational ages - extrapolation (Queenan, et al, 1993)
- Bilirubin normally peaks at 23-25 weeks

From Queenan, et al, 1993
Management of Rh Immunization

• Until recent years, mainstay of evaluation has been amniocentesis.
• With history of hydrops or fetal demise, early amnio (16-18 weeks) for Δ OD 450 is indicated
• Start amnios when critical titer is reached with timing of serial amnios based on Liley curve
• Ultrasound to evaluate for hydrops
• PUBS if hydrops, or upper zone 2 (lower threshold for Kell disease)

Management of Rh Immunization, con’t

• IUT if anemic (HCT< 30%)
• HCT drops about 1% / day
• Continue fetal monitoring and ultrasound between IUT’s
• Timing of delivery controversial in transfusion dependent gestations - 32-36 weeks
• Overall survival good - 88% total, 96% if no hydrops
  (Winnipeg data, Creasy & Resnik, 1999)

Management of Rh Immunization, con’t

• MCA Dopplers now being used in place of amnio
• Peak systolic MCA velocities are standardized by gestational age
• >1.5 multiples of the median corresponds to moderate to severe anemia
• Can avoid over 70% of invasive procedures using MCA peak velocities

What to Transfuse

• O negative donor blood or maternal blood
• Washed
• Irradiated
• Hematocrit > 80%
• CMV negative (preferable)
• CMV safe (acceptable)
How Much to Transfuse

- Many ways to calculate
- Several formulas which use gestational age, fetal weight, starting and target hematocrit
- Transfuse up to desired HCT (upper 40’s-50’s), less if hydropic (will need subsequent procedure)
- 50 cc/kg estimated fetal weight

Intraperitoneal Transfusion

- Rarely used today
- Survival with intravenous transfusion better than with intraperitoneal (Harman et al. 1990)
- Some advocate a combination of IPT and IVT (Moise et al. 1989)
- One advantage is slow absorption over several days leads to more stable fetal HCT
- Considered second line therapy

Other Blood Group Antigens Causing Hemolytic Disease

- ABO hemolytic disease - uncommon, usually mild, not evident until after delivery
- Anti-Kell - usually due to transfusion. Δ OD 450 can be falsely low, so low threshold for PUBS.
- Anti-c
- Anti-E
- Long list of other antigens (at least 43) which can cause hemolytic disease, but less clinically important than above

Risks/Complications of Cordocentesis

- Fetal Loss - risk variable depending on condition of fetus, overall 1-2%, range <1% - 50%
- Bradycardia - common but usually transient
- Bleeding - usually transient and mild
- Preterm Labor
Risks/Complications con’t

• Preterm Rupture of Membranes
• Infection - rare
• Cord Hematoma - rare, much more common with infusions
• Maternal Alloimmunization - largely preventable with Rhogam
• Failed Procedure

Technique

• Ultrasound Guidance
• Target - umbilical vein - cord insertion site vs free loop
• Confirm sample is fetal (MCV)
• Saline flush
• Fetal paralysis for transfusion
• Watch cord for bleeding after procedure

Fetal/Placental Surgical Procedures

• Open procedures are investigational - performed only at a few centers
• Most data on open fetal surgery comes from UCSF, CHOP, Cincinnati, where the majority of these procedures have been performed
• Some less invasive procedures are more commonly performed

Examples of malformations that may benefit from in utero surgical correction

• Twin twin transfusion
• Bladder outlet obstruction (posterior urethral valves)
• Diaphragmatic hernia
• Cystic Adenomatoid Malformation (CAM)
• Sacrococcygeal Teratoma
• Tracheal atresia/stenosis
• Neural tube defects
Bladder Outlet Obstruction

- Most commonly posterior urethral valves
- Male gender, dilated urinary tract, frequent oligohydramnios, 1 in 5-8000 births
- 15-40% with other anomalies or abnormal karyotype (Holzgreve & Evans, 1993)
- Massive bladder distention, followed by compensatory hypertrophy of the bladder wall usually requires postnatal surgical reconstruction
- Reflux hydronephrosis eventually leads to type IV cystic dysplasia and renal insufficiency
- Death usually due to pulmonary hypoplasia from long standing oligohydramnios

Posterior Urethral Valves - Surgical Approaches

- Vesicoamniotic shunts - double pigtailed catheter placed under ultrasound guidance
- Open surgical correction in utero - small numbers
- Fetoscopic shunt placement - investigational
Vesicoamniotic Shunts

- Careful selection of candidates for antenatal intervention is important to ensure that procedures to relieve LUTO are offered only to fetuses with sufficient renal function.
- Serial vesicocenteses are performed to evaluate fetal renal function, and the following parameters are used to indicate good prognosis:
  - Sodium<90 mmol/L
  - Chloride<90 mmol/L
  - Osmolality<180 mOsm/L
  - Total protein<20 mg/dL
  - β2-microglobulin<6 mg/L

- A shunt is placed across the fetal abdomen into the bladder draining urine into the amniotic space allowing drainage of the upper urinary tract and thus preventing pulmonary hypoplasia and physical deformations.
- In available studies, fetuses with posterior urethral valves had better outcomes but up to half of survivors have chronic renal insufficiency in childhood.
- A multicenter randomized trial has been proposed to better evaluate this therapy. The suggested trial will be known as the PLUTO trial.

Congenital Diaphragmatic Hernia
Congenital Diaphragmatic Hernia

- Usually a sporadic anomaly that is an isolated anomaly in 50% of cases
- Occurs in 1 per 2,000-5,000 live births
- Bowel in the chest leads to compression of lungs and pulmonary hypoplasia and hypertension
- Overall mortality with isolated CDH is 60-70%
- Again, animal models show promise for surgical intervention in utero
- Several procedures proposed (tracheal occlusion, open repair)
- Human results show no improvement in survival

Congenital Diaphragmatic Hernia

- Left-sided CDH (LCDH) can be evaluated on the basis of the presence of herniation of the left liver lobe into the thorax.
- Evaluation is made based on derivation of the lung-to-head ratio (LHR) during midgestation.
  - LHR > 1.6 equals survival of 83%
  - LHR < 1.6 equals survival of 66%
  - LHR = 1.0 is associated with an only 11% survival rate to time of discharge
**Congenital Diaphragmatic Hernia**

- Tracheal occlusion (TO) prevents egress of tracheal fluid
- Increasing lung tissue stretch.
- A randomized controlled trial comparing fetal endoscopic TO with standard postnatal care demonstrated no benefit from prenatal intervention.
- European FETO trial underway, preliminary data suggests balloon occlusion of the trachea increases survival in poor prognosis fetuses.

**Congenital Cystic Adenomatoid Malformation (CCAM)**
**Congenital Cystic Adenomatoid Malformation (CCAM)**

- Benign hamartoma of fetal lung - overgrowth of terminal bronchioles
- Variable presentation from small mass and good prognosis to large mass with pulmonary hypoplasia, polyhydramnios and hydrops
- Once hydrops present, mortality approaches 100%
- Surgical approaches include shunt placement and open resection
- Numbers are small, data very limited

**Twin-Twin Transfusion Syndrome**

- Occurs in monochorionic twins
- Vascular communication in placenta results in imbalance of blood flow
- 5-15% of monochorionic twins
- Donor fetus hypoperfused
- Recipient twin hyperperfused
- The donor twin often develops IUGR and oligohydramnios, whereas the recipient experiences volume overload and polyhydramnios that may lead to heart failure and hydrops.

**Sonographic Diagnosis**

- Polyuric Polyhydramnios in the Recipient
- Deepest vertical pocket of > 8 cm before 20 wks
- Deepest vertical pocket of > 10 cm after 20 wks
- Oliguric oligohydramnios in the Donor
- Deepest vertical pocket < 2 cm
- Growth restriction may coincide but is not part of the diagnostic criteria
### Twin-Twin Transfusion Syndrome, Quintero's Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Polyhydramnios/oligohydramnios with donor bladder visible</td>
</tr>
<tr>
<td>2</td>
<td>Donor bladder not visible</td>
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<tr>
<td>3</td>
<td>Presence of either absent or reverse end diastolic velocity of the umbilical artery, reverse flow in the ductus venosus, or pulsatile umbilical venous flow in either twin</td>
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<tr>
<td>4</td>
<td>Hydrops in either twin</td>
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<tr>
<td>5</td>
<td>Demise of one or both twins</td>
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### Twin-Twin Transfusion Syndrome - Therapy

- Serial reduction amniocenteses
- Septostomy
- Photocoagulation (LASER) of anastamoses via fetoscope
- Selective fetocide

### Twin-Twin Transfusion Syndrome - Therapy

- LASER procedure now considered first line therapy
- Major Complications of Fetoscopic Laser Coagulation
  - Postoperative single IUFD occurs in 33% of cases and double IUFD in 4% of cases
  - 60% are diagnosed within 24 hours
  - 75% are diagnosed within one week
  - PPROM
  - Isolated intertwin hemoglobin discordance
  - Persistent TTTS affects 14% of pregnancies where both fetuses survive one week post procedure
- Neurologic outcomes better than other therapies
- Serial amnioreduction
  - Reduces Polyhydramnios therefore reducing intrauterine pressure alleviating symptoms and prolonging pregnancy
  - May temporarily improve fetal hemodynamics by reducing the amniotic fluid pressure and thereby enhancing uteroplacental perfusion
  - PPROM or Abruptio Rate of 1-4% per intervention
  - Does not alter angioarchitecture therefore it must be repeated
  - The risk of a single IUFD carries with it also the risks of fetofetal hemorrhage and it’s consequences
  - Performs poorly in Stage 3 and 4
  - Overall perinatal survival rate of 61%
Twin-Twin Transfusion Syndrome - Therapy

- Septostomy
  - Benefits
  - Intentional puncturing of the intertwin septum w/o or w/ amnioreduction
  - Similar rates of survival of at least one twin
  - More likely to require only a single procedure
- Risks
  - Cord entanglement resulting from an iatrogenic monoamnionic state
  - Laser coagulation of the vascular anastomoses technically more challenging

Twin-Twin Transfusion Syndrome - Therapy

- Selective fetocide
  - Usually performed by umbilical cord coagulation with laser or bipolar energy
  - Should be reversed for cases with:
    - Severe discordant anomalies
    - Inaccessible vascular equator
    - PPRM of one sac
    - Imminent IUFD
- Results
  - Overall survival rate of the remaining twin is about 70-80%
  - Maximum survival rate is 50%

Other experimental surgical procedures

- Balloon valve dilation
- Sacrococcygeal teratoma
- Sealing membranes