The Fetus as our Patient: Therapeutic Advances in Prenatal Diagnosis & Therapy

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Outline

I. Historical Perspectives
II. Development of the Fetus as our patient
III. Therapeutic Options

I. Development of the Fetus as our second patient

- Fantastic advances in human embryology in 19th century
- Moral theory of personhood
- Discovery of the 46 chromosomes by Dr LeJeune along with Trisomy 21 as the source of Down's syndrome
- The advent of diagnostic ultrasound in the last 30 years giving us a fantastic window to the womb
- Technological advances in therapies for newborns
- The new science of "in utero therapy"

The New Science of "in utero therapy"

- Dr William Liley and in-utero transfusions for Rh disease in the 1960's using fluoroscopy
- Prenatal diagnosis of anomalies/conditions in utero that could be treated

II. In-Utero Therapies

- Bladder Outlet Obstruction
- Isoimmune Hydrops Fetalis
- Infectious Hydrops Fetalis
- Congenital Diaphragmatic Hernia
- Congenital Cystic Adenomatoid Malformation (CCAM)
- Neural Tube Defects (NTD)
- Sacrococcygeal Teratoma
- Severe Combined Immunodeficiency Syndrome
- Twin-twin Transfusion Syndrome (TTTS)
- Fetal Arrhythmias
- Hypoplastic Left Heart Syndrome

III. Therapeutic Options: Bladder Outlet Obstruction

- Results usually from incomplete cannulization between the pelvic and distal urogenital sinus
- Incidence is 1/5000-1/8000 male fetuses
- Babies die from pulmonary hypoplasia with decreased amniotic fluid
- Fetal urinalysis provides prognosis

Fetal urinary biochemsitry for good prognosis (after Glick, Nicolaides, Mandelbrot, and Johnson MP)

Chemical	Measurement
Sodium*	<100 mg/dL
Chloride*	<90 mg/dL
Osmolality*	<200 mg/dL
Calcium†	<8 mg/dL
β_2-Microglobulin‡	<4.0 mg/L
Total Protein§	<20 mg/dL

Bladder Outlet Obstruction

- Good prognosis includes:
  - Urine sodium < 100 Meq/liter
  - Urine chloride < 90Meq/liter
  - Urine osmolality < 200 milliosmo/liter
  - Beta-2 microglobulin < 6 mg/liter
- Algorithm requires three sequential urine samples 48-72 hours apart
- Place double pig-tail vesicoamniotic shunt to drain bladder
- Does not necessarily solve renal dysplasia
  - Prevents pulmonary hypoplasia
  - 33-50% risk of renal failure in childhood
  - Possible role in renal biopsy of fetus

Obstructive uropathy (Callen pg 765)

Ultrasound Findings	Favorable Prognostic Indicators	Unfavorable Prognostic Indicators	Prenatal Workup	Associated Anomalies
Anteroposterior diameter of the renal pelvis >10 mm For urethral obstruction; ureterectasis, vesicomegaly, a thickened bladder wall, and posterior urethral dilation Keyhold sign with posterior urethral valves Cystic renal parenchyma Thinning of renal cortex Echogenic renal parenchyma	Normal to moderately decreased amniotic fluid volume Normal renal parenchyma on ultrasound Normal fetal urinary electrolytes: Sodium, <100 mEq/L Chloride, <90 mEq/L Osmolality, <210 mOsm/L Beta$_2$-microglobulin, <2 mg/L	Severe oligohydramnios, especially with onset in the second trimester Increased echogenicity and cystic changes of the kidneys (cortical cysts) Abnormal fetal urinary electrolytes: Sodium, >100 mEq/L Chloride, >90 mEq/L Osmolality, >210 mOsm/L Beta$_2$-microglobulin, >2 mg/L	Fetal urinary electrolytes (to assess current renal function bladder tap is performed twice with an interval of 24–48 hours, examine second specimen) Karyotype Detailed sonogram	Ureteropelvic junction obstruction: other anomalies of the urinary tract in 27% Extraurinary anomalies: neural tube defects, imperforate anus, and Hirschsprung's disease Urethral obstruction: other anomalies of the genitourinary tract such as duplication of the urethra, hypospadias, and megalourethra; an association with chromosomal abnormalities (trisomy 18, 13, del 2q) has been reported[86]

Isoimmune Hydrops Fetalis

- Triumph of science going from 43.3/1000 samples in 1967 to 2.6/1000 samples in 1996 after Rh immune globulin at 28 weeks and post-partum
- Rh negativity
  - 15% Caucasian of European descent
  - 8% African-Americans
  - 8% Hispanics from Mexico/Central America
  - <1% in Eskimo, Native American, Chinese, Japanese

Isoimmune Hydrops Fetalis

- Test for Rh Antibody
  - Critical titer 1:8 to 1:32
  - Need 4 fold rise from base (monthly)
  - Test paternal Rh status/zygosity
  - Fetal blood type on amniocentesis (98+%)

Isoimmune Hydrops Fetalis

- Used to do amniocentesis for titers at 18-22 weeks and use curves-uses 3 zones to determine critical values
- Fetal blood sampling to determine Hct < 30% or 2 standard deviations below mean for gestational age
- Now use ultrasound (<35 weeks) with peak middle cerebral artery velocity (MCA) to determine need for sampling or delivery-98% accurate at >1.5 MoM (multiples of median for gestational age)

Isoimmune Hydrops Fetalis

- Intravascular transfusions now done for fetuses with Hct < 30% (as early as 18 weeks)
  - Use doppler/amnio data
  - Enter cord at placental insertion if able
  - Obtain opening Hct and transfuse to Hct 35-40%
  - Hct degrades about 1%/day so multiple procedures often necessary
  - Most babies delivered between 35-37 weeks with last transfusions at 30-32 weeks

Infectious Hydrops Fetalis

- Two most common are toxoplasmosis and Parvo-B19
- Toxoplasmosis seroconversion may take 1-4 months and carries risk of infection in fetus of:
  - 15% first trimester
  - 25% second trimester
  - 65% third trimester

Infectious Hydrops Fetalis

- Diagnosis of toxoplasmosis is by maternal blood testing for IgM (acute infection) and IgG (previous infection)
- Fetal infection may represent ultrasound findings of :
  - Hydrops
  - Cerebral calcifications
  - Liver calcifications

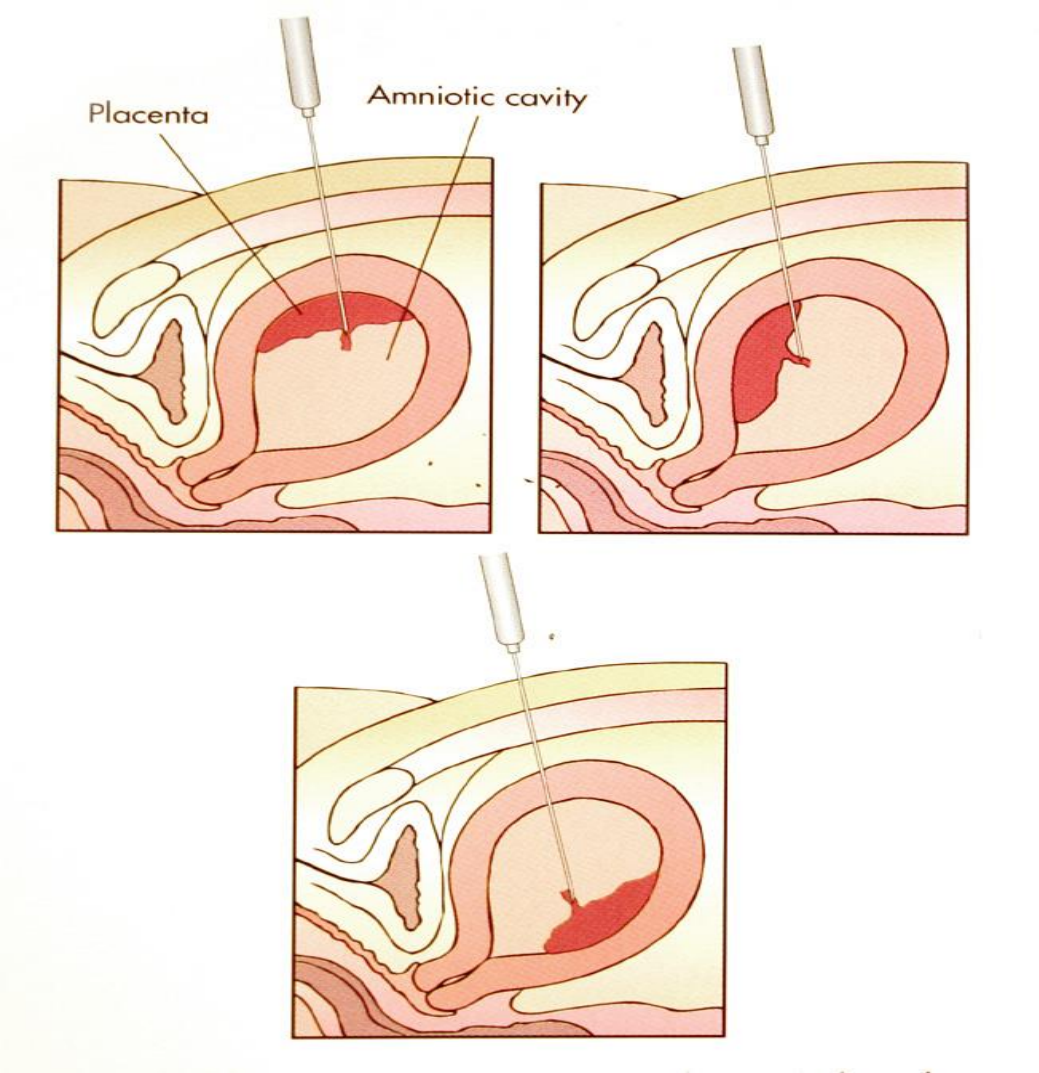
Infectious Hydrops Fetalis

- Diagnosis in fetus may be done with amniocentesis with DNA-PCR on amniotic fluid (sensitivity of 95%)
- Treatment in-utero with antibiotics (spectinimcyin and sulfas) has been successful in at least one case of hydrops

Infectious Hydrops Fetalis

- Parvo-B19 is more common than thought and has been seen in 10-15% of previously undiagnosed cases of hydrops
- Viral transmission rate is about 30% and risk for fetal death is 5-10% of that so risk is < 1% for fatality.
- Hydrops result of bone marrow suppression by the virus

Cordocentesis paths (after Hagen-Ansert pg 697)



Infectious Hydrops Fetalis

- Diagnosed by positive IgM (acute infection) in maternal serum
- Follow with serial weekly ultrasounds for 8-12 weeks to rule out hydrops
- Hydrop changes or increased dopplers (MCA) necessitate IVT
- Data shows that IVT survival after hydrops diagnosis 84% where observation survival was only 70%

Congenital Diaphragmatic Hernia

- Occurs in 1-4.5/10,000 live births
- Male/female equally affected
- Left sided 75-90%, right side-10%, and bilateral < 5%
- Unknown etiology but failure of closure of pleuroperitoneal canals
- Diagnosed antepartum most commonly by ultrasound with fluid in fetal chest

Congenital Diaphragmatic Hernia

- Mortality in unselected cases 80%
- Prognosis related to:
  - Large size
  - Diagnosis at < 24 weeks
  - Liver above diaphragm
    - Liver above survival 43%/ECMO 53%
    - Liver below survival 93%/ECMO 19%
  - Small contralateral lung
  - Associated anomalies
  - bliateral

Congenital Diaphragmatic Hernia

- Originally tried open repairs in-utero with varied success-with liver above diaphragm often "kinked" the umbilical/portal vein causing death
- Now have a NIH trial at San Fransisco to try fetoscopic tracheal occlusion
  - Use videofetoscopic technique to occlude trachea
  - Use ex utero intrapartum treatment (EXIT) procedure to partially deliver baby by c-section, tracheal clip identified by string and removed, and fetus intubated-success rates in 8 fetuses so far are 75% versus traditional surgery post-delivery.

Congenital Cystic Adenomatoid Malformation (CCAM)

- CCAM is a hamartomatous pulmonary lesion seen on ultrasound as a cystic mass
- Usually unilateral, may involve either lung and any lobe but usually is isolated to one lobe or segment in about 95% of cases.
- Bilateral in < 2% cases
- Three types:
  - Macrocystic (cysts 2-10 cm) (60% includes medium cysts)
  - Medium size cysts (cysts < 2 cm)
  - Microcystic (cysts < 0.5 cm) (40%)

Congenital Cystic Adenomatoid Malformation (CCAM)

- Appear as solid or mixed cystic/solid
- Often seen at 16-22 weeks and most regress by third trimester (100% fetuses with regression survive)
- Hydrops is very poor sign (100% mortality if treated expectantly)
- Medistinal shift is indication to attempt to tap a large mass in utero and even place an indwelling double pig-tail catheter
- May need to have in utero resection with open procedure (61% survival compared to 100% mortality with expectant management)

Neural Tube Defects (NTD)

- Occur in roughly 1/1000 pregnancies
- Related to folate deficiency
- Incidence reduced by about 50% with 400 mcg folate/day preconceptually in women without risk factors
- Need 4 mg/day preconceptually for patients with a family history of an NTD

Neural Tube Defects (NTD)

- Diagnosis by elevated MSAFP
- Seen on ultrasound with classic signs
  - “Lemon sign” with collapse of cerebral hemispheres
  - Dilated posterior fossa with Chiari II malformation
  - Open neural defect in spine

Clinical Aspects NTD's

- Anencephaly is lethal with no cerebrum
- Spina Bifida is variable
  - NIH Managemet Of Myelomenigocele (MOM) Study
  - There were 3 sites: Childrens' in Philadelphia, Vanderbilt, and San Francisco originally to include 200 patients (www.spinabifidamoms.com) (100 each arm)
  - Wanted to see if in utero surgery changes outcomes

Neural Tube Defects (NTD)

- Management of Myelomeningocele Study or “MOMS” study
  - Inclusion Criteria
    - Highest lesion T1 through S1
    - Hindbrain herniation (Chiari II malformation) by MRI
    - Maternal age 18 or older
    - Gestational age 19 0/7 to 25 5/7 weeks for randamization

Neural Tube Defects (NTD)

- Management of Myelomeningocele Study or "MOMS" study
  - Major Exclusion Criteria
    - Non-resident of US
    - Multifetal pregnancy
    - Obesity with BMI > 35
    - Abnormal karyotype or other anomalies
    - Current or planned cerclage, incompetent or short cervix documented
    - preterm labor, placenta previa or abruption
    - History of spontaneous preterm birth < 37 weeks
    - Maternal HIV/AIDS, Hepatitis B or C
    - Uterine anomaly or contradiction to surgery or anesthesia
    - Unable to travel or make follow up at 12 and 30 months

Results for MOM study[16]

- Trial stopped in 2010 at 183/200 patients for efficacy by analysis.
- 78 with prenatal surgery/80 postnatal surgery-all matched
- 2 primary outcomes: shunting& mental/motor function
- Decreased risk for shunting with prenatal surgery (40%) versus postnatal surgery (82%). ($P<0.001$)
- Improved composite score for mental & motor development with prenatal surgery compared to postnatal surgery. ($P<0.007$).
- Secondary analysis for ambulation at 30 months also improved in surgery group

Results for MOM study[16]

- Ambulation without orthotics was improved with 42% vs 21% bewteen groups.(P=0.01)
- Surgery patients had increased risk for preterm delivery < 37 weeks (79% vs 15%) and uterine dehiscence at delivery.

Sacrococcygeal Teratoma

- Most common tumor of fetus and neonate
- Incidence is 1/40,000 births
- Malignant invasion is rare
- Mortality is due to high-output shunting with heart failure and hydrops with placentomegaly
- May also produce “mirror syndrome” with maternal findings that appear to mimic severe preeclampsia

Sacrococcygeal Teratoma

- Diagnosed as early as 14 weeks by US
- Seen as cuadal or intra-abdominal mass
- May be cystic, solid, or mixed in appearance on ultrasound
- Differential includes renal, ovarian, or myelomeningocele
- Doppler flow will assist in documenting affects of shunting

Sacrococcygeal Teratoma

- Careful monitoring is necessary and may need in utero intervention if failure presents
- The newest technique involves ablation of feeder vessels with a radiofrequency ablation probe.
- Small numbers so far (5 cases) appears that this new technique is superior to resection.

Severe Combined Immunodeficiency Syndrome

- Severe Combined Immunodeficiency Syndrome (SCIDS)
- X-linked recessive, autosomal recessive, or as a sporadic form
- Absence of both B-cell and T-cell immunity
- Death by viral or bacterial infection within a year of age (“bubble children)

Severe Combined Immunodeficiency Syndrome

- Thought to be due to failure of hematopoietic stem cells
- Fetus is immune incompetent and therefore able to be transfused with maternal stem cells without a graft-versus-host rejection (usually fetus is immune competent by 14 weeks)
- Take maternal stem cells from bone marrow and infuse them with IVT into the fetus at 18+ weeks
- Infant is born as chimera with mix of maternal and fetal cells with immune competance and normal ability to fight infection

Twin-twin Transfusion Syndrome (TTTS)

- Most common problem with monochorionic twins with incidence 10-20%
- Defined as:
  - Growth discordance of 50+
  - Marked difference in amniotic fluid
  - Divergent fetal Hcts at birth

Twin-twin Transfusion Syndrome (TTTS)

- Major etiology thought to be shunting with vascular anastomosis between the twins-a “pump-donor” twin and a “recipient” twin
- The small donor twin often has severe oligohydramnios to anhydramnios with growth restriction
- The recipient twin has polyhydramnios and hydrops from volume overload

Twin-twin Transfusion Syndrome (TTTS)

- Ultrasound findings include:
  - Monochorionic twins
  - 50% discordance
  - Severe oligohydramnios donor (“stuck twin”)
  - Polyhydramnios in recipient
  - Unequal placental sharing
  - Arteriovenous communication by doppler

Twin-twin Transfusion Syndrome (TTTS)

- Favorable prognosticators (after Callen, Ultrasonography in Obstetrics & Gynecology, 4th edition, 2000)
  - Late-onset growth differences
  - Late-onset polyhydramnios
  - No hydrops
  - No placentomegaly
  - No cardiac failure

Twin-twin Transfusion Syndrome (TTTS)

- Unfavorable prognosticators (after Callen, Ultrasonography in Obstetrics & Gynecology, 4th edition, pg 776, 2000)
  - Early-onset growth differences (<20-22 weeks)
  - Early-onset polyhydramnios
  - Hydrops
  - Placentomegaly
  - Fetal cardiac failure

Twin-twin Transfusion Syndrome (TTTS)

- Workup includes:
  - Chromosomes
  - Detailed anatomy surveys for associated anomalies
  - Detection of vascular anastamosis

Twin-twin Transfusion Syndrome (TTTS)

- Therapies:
  - Serial amnio-reductions
  - Creation of window between membranes
  - Aggressive protein therapy for severe hypoproteinemia
  - Fetoscopic laser ablation of communicating anastomosis
    - Dr Julian De Lia of Milwaukee reports 153 total cases
    - Latest 67 cases from De Lia show:
      - Mean gestational age 21 weeks (range 18-24.5 weeks)
      - 55/67 (82%) one survivor and 94/134 babies surviving
      - 37 with surviving twins/18 one twin survivor/12 none
      - 4/93 (4.3%) with significant handicap with mean follow up of 60 months (range 48-84 months)

Twin-twin Transfusion Syndrome (TTTS)

- TTTS Foundation:
  - National Office
  - Longbeach Parkway
  - Bay Village, Ohio 44140
  - Voice: 440-899-TTTS
  - Fax: 440-899-1184
  - website: www.tttsfoundation.org

Twin-twin Transfusion Syndrome (TTTS)

- Centers for referral:
  - Dr Julian De Lia, MD (creator of laser therapy)
  - St Joseph Regional Medical Center
  - 5000 West Chambers Street
  - Milwaukee, WI 53210-1688
  - Phone: 414-447-3535
  - Fax: 414-874-4506
  - Dr Rubin Quintero, MD
  - Florida Institute for Fetal Diagnosis and Therapy
  - 13601 Bruce B. Downs Blvd, Suite 160
  - Tampa, FL 33613
  - Phone: 888-338-2577
  - Fax: 813-872-3794

Fetal Arrhythmias

- Tachyarrhymias are 8% of fetal rhythm disorders
  - Treat before 32-34 weeks
  - Utilize maternal oral first line-therapy
    - digoxin
    - flecainide
  - Second line-oral therapy
    - Verapamil, procainamide, quinidine, and propanolol
  - Intravenous therapy
    - IVT infusion of adenosine to break tachycardia and possible loading therapy with digoxin

Fetal Arrhythmias

- Bradyarrhthymias seen in about 6% cases
  - Common with structural defects (53%)
  - Ventricular rate < 55 bpm fatal
  - Pacemakers needed post-delivery
  - Check for possible Sjogren Syndrome A or Sjogren Syndrome B antibodies as well

Hypoplastic Left Heart Syndrome

- Usually result of aortic or mitral dysplasia or atresia
- Autosomal recessive
- Recurrence risk:
  - One child-4%
  - Two children-25%

Hypoplastic Left Heart Syndrome

- Ultrasound shows small left ventricle
- Absent or small mitral valve or aortic valve
- Prognosis may be poor small ventricle
- Therapies include:
  - Norwood in usually 3 stages to re-construct left ventricle
  - Fontan to connect left atrium to tricuspid and right atrium to pulmonary artery
- In utero therapy is latest attempt
  - Involves early catheter placement to perform essentially a valvuloplasty to open the mitral or aortic valve
  - Still too early to tell if this will be the treatment of choice

Malformation	Effect on Development	Fetal Treatment
Urinary tract obstruction	Renal failure, respiratory insufficiency	Vesicoamniotic shunt
Congenital diaphragmatic hernia	Respiratory insufficiency, pulmonary hypertension	Fetoscopic tracheal occlusion
Sacrococcygeal teratoma	Hydrops, fetal demise	Interruption of major blood supply by tum debulking or radiofrequency ablation
Myelomeningocele	Chiari malformation, hydrocephalus, paralysis	Fetal surgical repair Cerebrospinal fluid leak occlusion
Placental vascular anomalies	Twin-twin transfusion, TRAP sequence	Fetoscopic laser ablation of vessels Fetoscopic umbilical cord ligation/division
Congenital cystic adenomatoid malformation	Respiratory failure, hydrops	Resection of tumor Fetoscopic debulking of tumor
Congenital high airway obstruction syndrome	Hydrops, tracheal occlusion	Ex utero intrapartum therapy procedure Fetoscopic tracheostomy
Fetal hydrothorax	Respiratory failure	Thoracoamniotic shunt
Amniotic band syndrome	Limb/digit amputation	Fetoscopic band disruption

TRAP, twin reversed arterial perfusion.

IV. Science Confirms Two Patients

- What do we do with terminally ill perinates?
- Turn to *"The Perinatal Hospice"*
- Demonstrate compassion not abandonment with hospice