TRANSFUSION THERAPEUTICS IN THE INNER SPACE

ADVANCES IN INTRA UTERINE TRANSFUSION

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INTRODUCTION

- HDFN common cause of perinatal mortality
- 1st foetal Tx in 1963 by Liley.
- Severely anemic foetus c Rh HDFN.
- Amniography & foetography done.
- Intraperitoneal Tx under X-ray guidance.
- More than 50 Ags asso. with HDFN.
- New era ushered c real time ultrasound.
- Intravascular IUT in 1981.
- Txs between 17-35 wks of gestation
- RBCs/Platelets/drugs Txed by this process
- Life saving in severely anemic foetus
- Positive effect on neonatal course
- Txed effectively
  - less jaundiced
  - mildly anemic
  - without hydrops
  - no significant hepatosplenomegaly
• Foetus closely monitored during/after Tx
• Serial assessment of foetus
• Optimal timing of Tx
• Hydrops when foetal Hb < 6-7 SD
TYPES OF IUT

- Intraperitoneal
- Intravascular
- Intracardiac
- Intrauterine BM transplant
INTRAPERITONEAL Tx (IPT)

- First IUT available
- Used rarely nowadays
- Donor cells placed in peritoneal cavity
- Absorbed into circulation of fetus -
  - Sub-diaphragmatic lymphatics
  - Thoracic duct
- Severe hydrops- Impaired absorption
- Not possible to assess foetal Hct
Used In Conditions

- IV access difficult
- Morbidly obese patients
- Cord insertion in posterior placenta
- Late gestation / very early gestation
- Enlarging foetus obscure access
- Massive hydramnios
- Cord not accessible
- Multiple foetuses
INTRA VASCULAR Tx (IVT)

• Superior to IPT.
• Performed by cordocentesis.
• Can assess foetal Hct before & after Tx.
• Umbilical vein / Intrahepatic vein.
• Umbilical vein with larger diameter preferred.
• Vein near cord insertion in placenta.
• Tx in intrahepatic vein ↑ foetal stress hormones.
• Puncturing free loop of umbilical cord.
• Risk of tearing during foetal movements.
IVT continued…

- Diameter of umbilical artery < that of vein
- Accidental puncture of Umbilical artery
  - Hematoma
  - Spasm
  - Bradycardia
- Premedication of mother relieves anxiety.
IVT continued….

- Foetal paralysis by IV/IM pancuronium.
- Prevents needle displacement.
- Threshold for Tx Hct < 30%.
- 20/22 G needle used.
- Deliver RBC/Platelet/Drug into circulation.
blood transfusion through the umbilical vein in the placenta

ultrasound transducer

placenta

umbilical cord

fetus

pubic bone

uterus

vagina

cervix

spine
INTRA CARDIAC Tx

- Rarely used as a last resort.
- Especially in very early pregnancy.
- Potential hazards-
  - Arrhythmias
  - Hemo pericardium
  - Cardiac tamponade
  - Asystole.
INTRA UTERINE BM TRANSPLANT

- Congenital conditions
- Perinatally ased
- Leading to
  - Inadequate hemopoiesis
  - Increased destruction of cells

- Donor
  - Human BM
  - Foetal liver
  - Foetal Thymus

- Contain totipotent stem cells.
INTRA UTERINE BM TRANSPLANT   Contd....

- Attempts on research basis only.
- Conditions
  - *Rh allo immunisation*
  - *B and α thalassemia*
  - *SCID*
  - *Hurler syndrome*
  - *Chediak-Higashi syndrome.*
INDICATIONS FOR IUT

• Foetal allo immune hemolytic anemia
• Foetal allo immune thrombocytopenia
• Parvo virus B 19 infections
• Massive foeto-maternal hemorrhage.
• Twin to Twin Tx syndrome (TTTS)
• Twin Anemia Polycythemia Sequence (TAPS)
INDICATIONS FOR IUT -continued-

- Homozygous α thalassemia
- Congenital dyserythropoietic anemia
- Thrombocytopenia-absent radii (TAR)
- Placental chorioangioma
- Pure red cell aplasia
ALLO IMMUNE HEMOLYTIC ANEMIA

- Mother sensitised by RBC Ags.
- IgG Abs cross placenta
- Destroy foetal RBCs
- Rh HDN more common
- Other Abs implicated:
  - $Rh^c/C$
  - $Rh^e/E$
  - $K_1(Kell)$
  - $Fy^a/Fy^b$
  - $Jk^a$

- Foetal anemia, Hydrops, IUD
ALLO IMMUNE THROMBOCYTOPENIA

- Seen in 0.3% pregnancies.
- Detected after an affected sibling identified.
- Maternal antibodies against foetal platelet Ags.
- Abs involved
  - HPA 1a
  - HPA 1b
  - HPA 5b
  - HPA 3a
ALLO IMMUNE THROMBOCYTOPENIA  contd....

- 75-95% due to Anti HPA 1a.
- Abs against pvt / new Ags being discovered.
- Maternal ITP / SLE causative factor
- Risk of ICH 0%-1.5%
- ICH typically intra parenchymal.
PARVO VIRUS B19 INFECTION

- 27% of non immune hydrops
- Usually detected after dvpt of hydrops
- Arrest maturation of hematopoietic stem cells.
- Anemia/Thrombocytopenia
- Platelet count < 50,000/µl.
- May cause CNS damage.
- ▲ Serologic tests/DNA analysis
MASSIVE FOETO-MATERNAL HEMORRHAGE

- Non specific clinical symptoms
- ↓ Foetal movts.
- Sinusoidal foetal heart rate
- ↑ Blood flow velocity in MCA
- Anemia / Hydrops / IUD
TWIN TO TWIN TRANSFUSION SYNDROME (TTTS)

- Mono chorionic twins affected
- Chronic form of feto-foetal Tx.
- Discordance in amniotic fluid vol.
- Discordant birth weight & Hb levels
- Severe anemia in one of the twins
- Polycythemia in other twin
- Twin anemia polycythemias sequence (TAPS)
TWIN TO TWIN TRANSFUSION SYNDROME (TTTS) contd.

- Complications:
  - Limb necrosis
  - Cerebral injury
  - Perinatal death
HOMOZYGOUS α THALASSEМИA

- Defective α chain
- Serious condition
- Foetal anemia, Hydrops, death.
- IUT/Stem cell transplantation.
CONGENITAL DYSERYTHROPOIETIC ANEMIA

• May require IUT
• Best modality of Rx
  ➢ Bone marrow transplant
  ➢ Gene therapy
THROMBOCYTOPENIA-ABSENT RADII (TAR)

- TAR syndrome
- Severe thrombocytopenia
- IUT \( \bar{c} \) platelets required
- ↑ rate of ICH
- Responsible gene recently discovered.
- Prenatal \( \Delta \) by recombinant DNA technology
PLACENTAL CHORIOANGIOMA

- Non Immune hydrops foetalis.
- 1% of pregnancies affected.
- Affects mother & foetus adversely.
- C/c. Placental insufficiency.
- Foetal growth restriction.
- Polyhydramnios / preterm labor.
- Foetal CCF & death.
PURE RED CELL APLASIA

- Severe anemia
- Cardiac failure / hydrops / death
- IUT improves outcome
PRC FOR IUT

- O Rh D neg. & Kell neg. PRC
- Fresh blood < 72 hrs old
- Leukoreduced
- Irradiated 2-3 hrs prior to Tx
- Free of extraneous plasma / other cells
- Negative for
- Infectious markers
- Offending antigens
- HbS
PRC FOR IUT contd. . . . . .

- Hct-75%-80%
- Compatible maternal serum
- Fresh maternal serum used every time
- X matched before each & every IUT
- Washed maternal RBC
- Frozen RBCs.
PLATELETS FOR IUT

- Compatible with maternal serum
- Conc./Irradiated/Leukoreduced
- Negative for
  - infectious markers
  - offending Ag
- Packed beyond usual conc.
- Supernatant plasma removed
- Resuspended in appropriate medium
Washed platelets from mother

Advantages

- Readily available
- ↓ risk of TTD to mother
- Prevent sensitization to new RBC / WBC Ags
FOETAL BLOOD SAMPLING (FBS)

- Cordocentesis / Puncturing intrahepatic vein
- Done as early as 20 wks
- 1-2ml blood aspirated.
- ABO & Rh blood grouping
- Evaluation of anemia / thrombocytopenia
- DCT on foetal cells.
- Direct & reliable method
- Useful in predicting severity
- Cumulative procedure related risk
- High chance for foetal loss (6%)
- Risk of emergency delivery (13%-17%)
PROTOCOL FOR FBS

- Leiden University Medical Center
- Experienced member of foetal medicine unit
- Cell counter in operating room
- Complete hemogram in 2 mts.
- Compatible PRC / Platelets kept ready
- Infused during procedure, if necessary.
TIMING OF IUT PRC

• Careful individual risk benefit analysis
• Obstetric history.
• Estimation of maternal Ab titre.
• Serial assessment of foetal anemia
• Foetal Hb < 6-7 SD → Hydrops
• Ideal IUT when Hb < 4-6 SD
• Weekly ultrasonographic evaluation
• Help early detection of hydrops
• Regular doppler studies
• Progressive anemia
  
  ➢ ↓ *blood viscosity*
  ➢ ↑ *Maximum systolic flow velocity*
• Reliable doppler parameter
• Middle cerebral artery peak systolic velocity
• Amniotic fluid bilirubin quantification
• Spectrophotometry used
TIMING OF IUT(PRC) contd. . . .

- Usually 1st time cordocentesis @ 26 wks
- Previous history - cordocentesis earlier.
- Usual interval bet IUTs 2-4 wks
- Sometimes every 7-10 days
- Depends on fall in Hct
- Mean fall in Hct. 1 % per day.
- Due to
  - Growth of foetus
  - ↑ foetoplacental blood vol.
  - Actual destruction of RBC.
TIMING OF IUT PLATELETS

- Antenatal protocol to prevent ICH
- Routine FBS as early as 20 wks.
- Assessment of patients at risk
- Sibling ṡ no H/o. ICH, Txed at 28-32 wks
- ṡ H/o ICH Txed at 12-18 wks
- Platelet count <20,000/µl→ICH
- Platelet Tx if count< 50,000/µl
- Effectiveness limited
- Short life span of platelets
- Tx required frequently
VOLUME & RATE OF Tx

• Based on foeto-placental blood vol.
• At any given gestational age.
• Others parameters to be considered

- Pre-Tx foetal Hct
- Hct of donor blood
- Estimated foetal weight
- Desired post Tx Hct
• Total volume Txed / IUT 20-120 ml
• Tx rate 5ml/kg/mt
• Time for each procedure 20-60 mts.
• Large volume Tx ↓ no. & frequency of IUT
• Minor ↑ in foetal bradycardia c large vol.
• Volume reduced & highly conc. Platelets
• < 30wks gestation 1- 5 ml Pl.Conc.
• > 30wks gestation 5-10ml Pl.Conc.
PROCEDURE

• Out patient procedure
• Done by team consisting of 3-4 members
• Mild sedation for mother
• IM/IV Pancuronium to foetus
• Induce foetal paralysis
• Prevent movts of foetus & needle jerking.
• Tx given usually between 17-35 wks
• Access foetal circulation ċ 20/22 G needle
• Under real time ultrasound guidance
PROCEDURE  contd....

• Aspirate blood for diagnosis
• Deliver RBC/Platelets/drugs
• Txed at a rate of 5 ml/kg/mt.
• Monitor blood flow & foetal heart
• PRC : 2\textsuperscript{nd} Tx 1-2 wks after 1\textsuperscript{st}
• Platelets: frequent Txs required
**TOP UP vs EXCHANGE IUT**

- **Top up IUT**
  - Directly Tx blood into fetus
  - Not removing blood from foetus in between
  - Circulatory overload.
  - Cardiac tamponade

- **Exchange IUT**
  - Aspirate small qty of blood from foetus
  - At regular intervals during IUT

- Umbilical venous pr: monitored routinely
- Change in pr: >10mm of Hg
- Small qty of blood removed from foetus
- Replaced by normal saline
COMPLICATIONS & MANAGEMENT

• a. Foetal heart rate abnormalities
  ➢ Tachycardia
  ➢ Bradycardia

• Stop Tx until resolution of abnormality
• If unremitting - plan delivery

• b. Preterm labour
  ➢ Tocolysis depending on situation
c. Preterm premature rupture of membranes
   - No vaginal examination
   - Non stress test (NST) by cardiotocography
   - Observation

d. Abruptio placenta
   - Mild - observation
   - Significant - Plan delivery

e. Inability to access umbilical circulation
   - Hepatic vein puncture
   - IPT
   - Cardiac puncture
COMPLICATIONS Contd......

• f. Umbilical cord hematoma
  ➢ *Emergent delivery*

• g. Direct fetal exsanguination
  ➢ *Excessive blood loss*
  ➢ *Emergent delivery*

• h. Foetal death
  ➢ *Delivery still born*
COMPLICATIONS Contd.....

• i. Chorioamnionitis
  - Plan delivery
  - Administration of antibiotics

• J. Tx reactions in mother
  - Symptomatic management

• k. Maternal abdominal wall / rectus hematoma
  - Surgery if pt. unstable from hemorrhage
1. Worsening of HDN due to
   - ↑ Transplacental hemorrhage
   - Other unknown factors

   - More IU Txs

2. Puncture of umbilical artery
   - Remove needle
   - Replace in umbilical vein
OUTCOME OF IUT

• Foetal erythropoiesis suppressed
• Completely dependent on IUT
• Txs required every 2-4 wks
• Multiple Abs develop in 70% females
• Fall in post Tx Hct unpredictable
• Mean fall in Hct 1% per day
• Stable decay of Txed cells
LIMITATIONS

• Identification of at risk pregnancy

• Not feasible to screen all pregnancies

• To detect RBC/Platelet Ab.
CONCLUSION

• Gold standard Rx for hydrops foetalis
• Careful individual risk benefit analysis
• IUT ↑ Survival rate of affected foetus
• Safe & successful nowadays
• IUT not available in many developing countries
• After IUT neonates require top up Tx for next 6 months
• Multiple allo Abs in mothers pose problems
• Routine screening for all Abs not yet established
CONCLUSION  Contd...

- Foetal thrombocytopenia detected very late
- FBS as early as 20 wks - detection of thrombocytopenia
- IUT required every 2-4 wks generally
- Sometimes every 7-10 days
- Timing of Tx important issue.
- Ideal post Tx Hct 30%-50%
- Sudden ↑ in foetal Hct → death
- Compromised foetal state itself → death.
- Plasmapheresis / IVIg- other modalities of Rx