Discordant fetal size & Fetal Anomalies (x5 pregnancy loss)

Prematurity 60% (11% <32w)
PNMM (x5 singleton)
IVH (x2) with 1% CP

Systematic sonographic evaluations provide a selective benefit for subgroups of Twins
ACOG Practice Bulletin 144, May 2014
Twins: Epidemiology & Pregnancy failure

- Natural Hx ~ 1 in 80 births with population variations dependent on familial factors, nutrition, maternal age, oral contraception discontinuation,..

- In the USA the incidence is ~3.3% births as result of: 1) ART (in 2010 26% of IVF patients had twins) and 2) pregnancies in older women (7% in women >40 y/o)

- Twins account for 10% of the Perinatal Mortality in the USA

- The prevalence of twins in early miscarriage is difficult to quantitate

- Perinatal Mortality:
  - 44 per 1000 in MC
  - 12 per 1000 in DC

Norwitz ER, Controversies in multiple gestation, 1997
Livingsgton JE & Poland BJ. A study of spontaneously aborted twins. Teratology 1980;21:139
Twin Pregnancies
"From public fascination to the relevance for patients and society"

1) ~83% of patients with twin pregnancies compared to 32% in singletons will develop Hyperemesis, Hypertension, Diabetes, Anemia, IUGR, Prematurity, Intrapartum dystocia, Venous thrombosis (x2), Post-partum hemorrhage

2) Twin pregnancies have higher rate of Genetic and Congenital anomalies than singletons (selective terminations and reductions from higher order pregnancies

3) Increased risk for placental disorders causing a “vanishing twin”, miscarriage, IUFD, discordant fetal growth, TRAP, TTTS, Abruption (5%), SGA, PTD, Cesarean delivery and Neonatal death

4) At least (x2) the health care cost per newborn with an increased risk for long term residual neuro-developmental pathology when compared to singleton pregnancies matched for gestational age at delivery

5) Increased risk for post partum Depression and emotional distress in the family

Santolaya and Faro. Clinical Obstetrics and Gynecology, March 2012
Stepwise approach to the Sonographic evaluation in Twin Pregnancies

1. Review Hx of spontaneous vs. ART/IVF-PGD / maternal age, medications, maternal health
2. 1st trimester diagnosis of fetal heart activities, chorionicity, amniotic sacks, cord insertions, cervical length, location of pregnancy, uterine/pelvic masses, discordant size
3. 1st and 2nd trimester serial screening for genetic/congenital anomalies/ discordant size
4. Prematurity: cervical length, fetal size discordance, fetal presentation - time intervals depending on chorionicity -.

Hubinnot & Santolaya, Am J Perinatol, 2010;
First trimester evaluation: # of placental masses and the “Lambda sign” will identify Dichorionic pregnancies with 97.4% sensitivity and 100% specificity Sepulveda et al 1996

- 70% of all Twins are DZ resulting from a double ovulation: formation of 2 gestational sacs (DC) not necessarily adjacent.
- The prevalence varies depending on factors such as Maternal age and Ethnicity. Familial may result from higher than average rate of multi-ovulation.
30% of all Twins are MZ
-25% two placentas (DC)
-75% single placenta (MC ~1 in 400 births)

The prevalence is relatively constant worldwide

The close proximity of the cord insertions may increase the risk for complications due to vascular anastomosis

Compared to Di-chorionic twins those with only 1 gestational sac have an increased risk for PN Mortality & Morbidity


Mono-amniotic Twins

Can be recognized prior to 8 weeks gestation
*Bromley and Benacerraf, 1995*

US evaluation at 11-13+6 weeks can exclude a dividing membrane
*Shen et al, 2006
Sherer, 2002*

Early diagnosis of a co-existing molar pregnancy is an essential step
*Wee and Jauniaux 2005. Sumigama et al 2007*
Mono-Amniotic Twins
“Cord Entanglement”

During the 1\textsuperscript{st} trimester

During the 2\textsuperscript{nd} trimester

Personalized Medicine including the option of admission to Hospital after 24 weeks, steroids, continuous monitoring with daily BPP & Umbilical Cord Doppler and Fetal growth assessment (x 2w) until delivery ~ 34w
Stepwise approach to the sonographic evaluation in Twins

1. Hx of spontaneous/ ART/IVF-PGD / medications / maternal health
2. 1st trimester diagnosis of fetal heart activities, chorionicity, amniotic sacs, cord insertions, cervical length, location of pregnancy, uterine/pelvic masses
3. 1st and 2nd trimester serial screening for genetic/congenital anomalies
4. Prematurity: cervical length, fetal size discordance, fetal presentation - time intervals depending on chorionicity -.
Twins: Twice the trouble

Prematurity 60% (11% <32w)
PNMM (x5 singleton)
IVH (x2) with 1% CP

Discordant fetal size & Anomalies

Discordant fetal size

Concordance at 11-14w is defined by <10% difference in CRL
Tai and Grobman 2007

In MCDA Twins, CRL difference greater than 15% with discordant amount of amniotic liquor has been associated with and increased risk for TTTS, IUFD and >20% birthweight difference among co-Twins

~15% of MCDA pregnancies with 1 twin NT >95th centile have TTTS Sebire et al 2000 and abnormal Ductus Venosus blood velocity waveforms can improve detection rate Matias et al, 2005

Distance at the placenta cord insertions
Deducing the fetal genome using Maternal blood samples


- Direct gene analysis for RhD factor possible
- Direct analysis of Monogenic disorders inherited from the father possible
- Aneuploidy 21, 18, 13, X and Y analysis possible


Deducing the fetal genome using Maternal blood samples


In Twins Very Limited Evidence Based Supporting Data!


cfFDNA misses 50% of Chromosomal anomalies at term
Prenatal Genetic Screening in Twins
“A difficult Task”

Aneuploidy occurs in ~0.5% of Twin gestations
Sperling et al. 2007

More accurate Risk estimation for T21 by adding the absence of the nasal bone
Zoppi et al., 2003 and Cleary-Goldman et al., 2008

NT measurement alone can be used as a sensitive screening test for Genetic and Congenital abnormalities in twins

Mitotic Hetero Karyotypia in MC Twins requires UPD testing to R/O Chromosome rescue. Cheng et al., 2006 and West et al., 2003
### Prospective validation of the 1st Trimester Combined Screening test in DCDA Twins after IVF

<table>
<thead>
<tr>
<th></th>
<th>Mat Age years</th>
<th>CRL mm</th>
<th>FbhCG MoM per fetus</th>
<th>PAPP-A MoM per fetus</th>
<th>NT Twin A mm</th>
<th>NT Twin B mm</th>
<th>GA Delv weeks</th>
<th>Mean NBWt gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton N = 80</td>
<td>32 (5.4)</td>
<td>60 (7.1)</td>
<td>1.20 (0.6)</td>
<td>1.3 (0.8)</td>
<td>1.5 (0.4)</td>
<td></td>
<td>39.4 (1.0)</td>
<td>3441 (407)</td>
</tr>
<tr>
<td>DCDA Twins N = 19</td>
<td>35 (4.4)</td>
<td>62.4 (10)</td>
<td>1.05 (0.5)</td>
<td>1.2 (0.6)</td>
<td>1.4 (0.3)</td>
<td>1.6 (0.4)</td>
<td>34.6 (3.3)</td>
<td>2198 (604)</td>
</tr>
</tbody>
</table>

**P-value**

Singleton N = 80: 0.008*

DCDA Twins N = 19: 0.13

### Summary

1) Serum markers relate to the Pregnancy risk while NT is a Fetus specific risk
2) In DZ twins the Risk of each fetus is independent and CHORIONICITY (MC=MZ; DC=~90%DZ)
3) The “Pseudo Risk” estimation is THEORETICAL: the profile of MS markers in twins with aneuploidy are unknown

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Wald NJ and Rish S. Prenat Diagn 2005

Fracoise L, Santolaya J ,et al, ACMG 2013
Sonographic Markers for TRISOMY 21 in singletons using 3D-Volumes Acquired at 11-13w

<table>
<thead>
<tr>
<th></th>
<th>All (%)</th>
<th>Start with Profile (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT</td>
<td>83</td>
<td>90</td>
</tr>
<tr>
<td>Nasal Bone</td>
<td>65</td>
<td>78</td>
</tr>
</tbody>
</table>

Antoni Borrell, Julian N. Robinson, Joaquin Santolaya-Forgas.
NT from 3-D volumes Harvard Medical School. AJP 2009

FASTER: N.6234 with 11 T21. 76% “acceptable” Image. 2/11 T21 had Absent Nasal Bone.
DSR 7.7%. FPR 0.3%. PPV 4.5% Malone et al, OG 2004
Fetal thymic measurements in Twins
Down syndrome & Congenital Immunodeficiency

Thymic Diameter: 4.96 + 1.06 x Gestational Age (weeks)
(N: 904; S.D. 3.78; R² 0.91; p < 0.001)

Sensitivity: 68.2% (38.735 to 83.6)
Specificity: 95.4% (84.8 to 98.7)
Positive Likelihood Ratio: 15
Negative Likelihood Ratio: 0.33

Gestational age (weeks)

Fetal thymic measurements in Twins
Down syndrome & Congenital Immunodeficiency

Gamez, Santolaya et al, UOG, 2010
De Leon, Santolaya et al, PDx 2011

Sonographic Markers (Risk for DS)

- Femur/humerus x2
- Hydronephrosis x1.5
- EIF x2
- Nuchal Fold x18
- No marker x 0.5

Benacerraf, 1987
Nyberg, 1990
Vinzileos, 1997
Cardiac anomalies account for 68% of all the structural defects in twins. [Sperling et al 2007, Manning 2008]

Cardiac anomalies are more likely when increased NT measurement and abnormal DV waveforms are detected. [Maiz et al 2008]

Extrophy of the cloaca, Sacro coccygeal teratoma, Sirenomelia, Anencephaly, VATER sequence are more frequent in MC twins than DZ twins or singleton pregnancies. [Smrcek et al 2003, Bulbul et al 2004, Vandecruys et al 2006, Sperling et al 2007]

NOTE: The risk of miscarriage after selective TOP in DCDA Twins ranges from ~3% at 14 weeks to ~8% at 20 weeks gestation.
2-Distinct anomalies of Monozygotic Twins that should be Diagnosed during the 1st Trimester of pregnancy

Conjoined Twins:
2 and 3-D ultrasound with color flow can help define the degree of inter-twin vascular and organ sharing
Hubinont et al 1997, Pajkrt et al 2005

Acardiac/ Amorphic twin
Unidirectional arterio-arterial placental anastomosis: Twins with reverse arterial perfusion (TRAP) seen in both MCMA and MCDA twins
Santolaya and Faro. Clinical Obstetrics and Gynecology, March 2012
Management of MCDA Twins Discordant for a Major Anomaly

Selective fetal reduction by bipolar umbilical cord occlusion or US-guided obliteration procedures depends on Gestational Age and the experience of the operator.

**Post-hoc analysis of fetal anatomy in 3D-volumes acquired at 11-13w gestation**

<table>
<thead>
<tr>
<th>Systems evaluated in singletons</th>
<th>All (%)</th>
<th>Profile (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord insertion</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>Cranium and choroid plexus</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>Diaphragm and stomach</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>86</td>
<td>90</td>
</tr>
<tr>
<td>Bladder</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>Spine and kidneys</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Four chambers view</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Face</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Outflow tracts</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Procedure related risk for CVS and Amniocentesis depends on Gestational age, Chorionicity and Experience of the operator!


Consider Microarray Chromosomal testing in the case of Fetal anomalies
Stepwise approach to the sonographic evaluation in twins

1. Hx of spontaneous/ ART/IVF-PGD / medications / maternal health
2. 1\textsuperscript{st} trimester diagnosis of fetal heart activities, chorionicity, amniotic sacs, cord insertions, cervical length, location of pregnancy, uterus/pelvic masses
3. 1\textsuperscript{st} and 2nd trimester serial screening for genetic/congenital anomalies
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Prematurity 60% (11% <32w)
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Discordant fetal size & Anomalies
Prematurity

Temporal Changes in the Incidence of preterm births (20-37w) in the USA

- 9.4% in 1981
- 10.6% in 1990
- 11.6% in 2000
- 11.9% in 2010

Gestational age Distribution
USA National Center for Health Statistics, 2002

Perinatal Morbidity Including multiple + singleton gestations
Mercer B, Obstet Gynecol 2003
## Birthweight by fetal number

<table>
<thead>
<tr>
<th></th>
<th>Single</th>
<th>Twin</th>
<th>Triplet</th>
<th>Quadruplet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth &lt; 32 wk (%)</strong></td>
<td>1.6</td>
<td>12</td>
<td>36</td>
<td>60</td>
</tr>
<tr>
<td><strong>Birth &lt; 37 wk (%)</strong></td>
<td>10.4</td>
<td>58</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td><strong>Mean GA at Birth (w)</strong></td>
<td>39</td>
<td>35</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td><strong>BWT &lt; 1.5 kg (%)</strong></td>
<td>1.1</td>
<td>10</td>
<td>34</td>
<td>61</td>
</tr>
<tr>
<td><strong>BWT &lt; 2.5 kg (%)</strong></td>
<td>6.1</td>
<td>55</td>
<td>94</td>
<td>99</td>
</tr>
</tbody>
</table>

*Data from the CDC, 2002*
Stratification of Preterm Deliveries
(309 sets of MCDA Twins at >24w gestation)

Uncomplicated pregnancies (N=234)
TTTS (N=39)
Severe growth discordance (N=36)

Sonographic Uterine Volume at 11-14 w Gestation
“A measure of early adaptation to pregnancy”

DCDA Twins UV = 278.2 + 8.9 CRL
P<0.05

Singleton UV = 15.8 + 8.1 CRL
P<0.05

Uterine Adaptation to Pregnancy. Santolaya J et al. UOG& AIUM 2015
Prematurity & Cervix-placenta relationship

1. **Cervical length** of 15 mm in singleton gestations has a 50% risk of preterm delivery at <32 weeks of gestation *(Hassan SS, 2000)*, in Twins the same risk has been reported when the CL is 25 mm *(Souka AP, 1999)*

2. **Cervical length** of 20 mm at 20–24 weeks in asymptomatic women with Twins is a predictor of preterm birth at <32w (LR 10) and <34 w (LR9) *(Conde-Agudelo A, 2010)*


Can we prevent preterm birth in twin gestations?

Presently, there is no intervention that can reduce the rate of non-indicated birth at <32w, including cerclage, 17OHP-C (up to 500 mg x2 weekly), or a cervical pessary. In fact, P and cerclage may have adverse effects in twins.

Very limited data concerning procedures and drugs to prevent PREMATURITY in Twins: Bed rest, Cerclage, Amniocentesis to R/O inflammation/Infection, Antibiotics, Tocolytics? ACOG Bulletin #522, April 2012

**PREDICT CONTROLED TRIAL**

Vaginal Progesterone/Placebo (MC?) (UOG, 2011)

---

R/O Uterine anomalies, fibroids, pelvic masses, Ectopic pregnancy
Currently Twin births in the USA occur in ~1 in 30 pregnancies: 75% DCDA; 24.5% MCDA; 0.3% MCMA)

More than 3-fold PNMR in MC than DC and both greater PNMR than singleton pregnancies. MCMA have 15% PNMR

Death of 1 twin is associated with death of co-twin in 15% of MC and 3% of DC gestations. Neurologic deficits in 26% of MC and 2% of DC

Twins account for 45% of NICU admissions

In twin pregnancies serial sonographic evaluations from the 1st trimester are recommended by AIUM, ACOG: x2w MC and x3-4w DC

During the 1st Trimester (70%MZ/30%DZ) vs. Delivery (40%MZ/60%DZ) most likely due to ~20% overall vanishing twins prior to 14w due to uterine factors, congenital anomalies of the placenta/fetuses, teratogens…  Graham 2009

Twins: Twice the trouble

Ultrasound
Informatics/Web Access
Perinatology
Multidisciplinary
Genetics
Health Care Provider
Home

joaquinsantolaya@ufl.edu