The Management of Monochorionic-Diamniotic Twins

Part 2: Prenatal diagnosis and antenatal management

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Disclosures

• none
PRENATAL DIAGNOSIS & ANEUPLOIDY SCREENING IN TWINS
Twins – calculate the risk of aneuploidy by considering the maternal age related risk of aneuploidy, zygosity, and the probability that either one or both twins could be affected

- Discuss options for pregnancy management if one fetus is found to be affected (termination of entire pregnancy, selective termination, continuing the pregnancy)
INVASIVE TESTING IN TWINS

• Loss rate is ~3.5% when amnio is performed in twins (not higher than the background loss rate) – small series
• No data on loss rates after amniocentesis in high-order multiple gestations
• Similar information exists in small non-randomized series re CVS loss rates in twins
MONOCHORIONIC TWINS

- Likelihood of discordance in karyotype is low
  - Both fetuses SHOULD be either affected or unaffected
  - Exceptions possible
- Patients may opt for karyotype analysis on a single fetus
- Should discuss accuracy of chorionicity by ultrasound (most accurate at or before 14 weeks (98%))
Genetic Counseling

- Aneuploidy
  - Singletons: age related

- Dizygotic twins
  - Age related risk for anomalies is the same for each twin as for a singleton

- Monozygotic twins
  - Should be age related risk
“Advanced” maternal age...

- Singleton: age ≥ 35 at delivery
- Monochorionic twins: age ≥ 35 at delivery
- Dizygotic twins:
  - Literature review: age 31-33
  - ACOG: age 33
- Triplets, & high-order multiples: ?
- Insurance?

Obstet Gynecol 1997; 89:248-51
Semin Perinatol. 2005 Oct;29(5):312-20
Prenatal diagnosis options

Screening tests
- First trimester screening
- Second trimester MSAFP only
- Second trimester ultrasound screening
- Multiple marker screening

Invasive diagnostic tests
- Chorionic villi sampling
- Amniocentesis
First trimester NT screening

• Maternal age + NT screening
  – Valid from 10 4/7 to 13 6/7 weeks.
  – Sensitivity of NT alone in multiple gestations ranges from (68%-88%)
  – Detection of Down’s with multiples is similar to singletons
  – Not affected by ART or number of multiples

Sepulveda, Ultrasound Obstet Gyn 2008
DeVore, www.fetal.com
NT: Twin = Singleton

<table>
<thead>
<tr>
<th>Nuchal Translucency (Mean CRL)</th>
<th>N</th>
<th>Mean mm (+ SD)</th>
<th>Mean MOM (+ SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singletons (62.7 mm)</td>
<td>120</td>
<td>1.5 (+ 0.5)</td>
<td>0.9 (+ 0.5)</td>
</tr>
<tr>
<td>Twins (62.3 mm)</td>
<td>120</td>
<td>1.5 (+ 0.17)</td>
<td>0.9 (+ 0.4)</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Down’s Syndrome Screening

- Twins
  - Analytes valid
  - IUFD at >8 wks invalidates screening
- Higher order multiples
  - NT measurements only

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Risk for trisomy 21 at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Singleton</td>
</tr>
<tr>
<td>20</td>
<td>1100</td>
</tr>
<tr>
<td>25</td>
<td>1000</td>
</tr>
<tr>
<td>30</td>
<td>650</td>
</tr>
<tr>
<td>31</td>
<td>550</td>
</tr>
<tr>
<td>32</td>
<td>450</td>
</tr>
<tr>
<td>33</td>
<td>400</td>
</tr>
<tr>
<td>34</td>
<td>300</td>
</tr>
<tr>
<td>35</td>
<td>250</td>
</tr>
<tr>
<td>36</td>
<td>200</td>
</tr>
<tr>
<td>37</td>
<td>150</td>
</tr>
<tr>
<td>38</td>
<td>120</td>
</tr>
<tr>
<td>39</td>
<td>90</td>
</tr>
<tr>
<td>40</td>
<td>70</td>
</tr>
<tr>
<td>41</td>
<td>50</td>
</tr>
<tr>
<td>42</td>
<td>40</td>
</tr>
</tbody>
</table>
Nuchal Translucency
Monochorionic Twins

- NT obtained individually and averaged to give risk to pregnancy.
  - Concordant karyotype
  - Discordant NT measurement
- False positive rate increased to 8%
  - Thickened NT may be early TTTS
Nuchal Translucency in Twins
First trimester combined screening

Maternal age and NT + maternal serum free β-hCG and pregnancy associated plasma protein-A (PAPP-A)

- Twins: (5% false positive rate)
  - Monochorionic: ~84% detection rate for DS
  - Dichorionic: ~70% detection rate for DS
First trimester screening

• Pseudorisk approach:
  – Larger of the two crown-rump lengths-EGA
  – Sum the two NT likelihood ratios multiplied by the biochemical likelihood ratio to get the pregnancy specific risk

• Sensitivity of 75-85% in twins
  – False positive rate 5-9%

Semin Perinatol 29: 395-400
First trimester combined screening

• Criticism:
  – Abnormal serum levels from an affected fetus will bring overall serum levels closer to the mean by unaffected fetus
  – Unknown effect of ART on first trimester serum markers
  – Unclear on whether adding serum markers is superior to using NT alone
  – Statistical modeling
Second trimester MSAFP

- Used to screen for ONTDs
- Can be used in twin gestations
- Less reliable than singletons

<table>
<thead>
<tr>
<th>MOM (≥X)</th>
<th>Anencephaly (%)</th>
<th>Open spina bifida (%)</th>
<th>False positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>100</td>
<td>96</td>
<td>46</td>
</tr>
<tr>
<td>2.5</td>
<td>99</td>
<td>89</td>
<td>30</td>
</tr>
<tr>
<td>3.0</td>
<td>98</td>
<td>80</td>
<td>19</td>
</tr>
<tr>
<td>3.5</td>
<td>96</td>
<td>69</td>
<td>12</td>
</tr>
<tr>
<td>4.0</td>
<td>93</td>
<td>58</td>
<td>7.8</td>
</tr>
<tr>
<td>4.5</td>
<td>89</td>
<td>48</td>
<td>5.0</td>
</tr>
<tr>
<td>5.0</td>
<td>83</td>
<td>39</td>
<td>3.3</td>
</tr>
<tr>
<td>5.5</td>
<td>77</td>
<td>31</td>
<td>2.2</td>
</tr>
<tr>
<td>6.0</td>
<td>70</td>
<td>25</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Second trimester ultrasound

- Major structural abnormalities
- Soft markers (Likelihood ratio)
  - Nuchal thickening (11)
  - Echogenic bowel (6.7)
  - Short humerus (5.1)
  - Short feumr (1.5)
  - Echogenic intracardiac focus (1.8)
  - Pylectasis (1.5)
  - Sandal gap deformity
  - Absent nasal bone
- Absence may reduce DS risk 50%

Multiple marker screening

• Serum AFP, beta human chorionic gonatotropin (β-hCG), unconjugated estriol, and inhibin-A

• Singletons:
  – 77% detection rate, 5% false-positive

• Twins:
  – 47% detection rate, 5% false-positive

• Problems:
  – Normalization of serum values
  – Which fetus is anomalous?

Conflicting data:

- **O’ Brien et. al.**
  - 4443 twin pregnancies compared to >250,000 singletons.
    - Inconsistent results for the different analytes

- **Garchet-Beaudron et. al.**
  - Prospective study of second-trimester maternal serum markers
  - 11,040 twin & 64,815 singleton pregnancies
    - Mean detection rate was 63%
      - 74.4% in singletons.
    - False-positive rates: 10.8% in twins vs 10.3% in singletons (NS).

Prenat Diagn. 2008 Nov 11;28(12):1105-1109
Live-Born Down Syndrome Prevalence

- Live-born twin Down syndrome (DS) prevalence only 18% higher than singletons.¹

- Population-based study of 106 twin DS live births only 3% > singletons.²

## Down Syndrome Detection Rate in Twins by Chorionicity at a 5% FPR

<table>
<thead>
<tr>
<th>Twin Pregnancy</th>
<th>NT Alone (%)</th>
<th>Combined Test (%)</th>
<th>Integrated Test (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monochorionic-diamniotic</td>
<td>73</td>
<td>84</td>
<td>93</td>
</tr>
<tr>
<td>Dichorionic-diamniotic</td>
<td>68</td>
<td>70</td>
<td>78</td>
</tr>
<tr>
<td>All twins</td>
<td>69</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>Singleton</td>
<td>73</td>
<td>85</td>
<td>95</td>
</tr>
</tbody>
</table>

Wald et al. Prenat Diagn 2003; 23:588-592
Invasive testing

- CVS
- Amniocentesis
CVS

- Sampling of chorionic villi for DNA or chromosome analysis
- Transcervical or transabdominal, under ultrasound guidance
- Done between 10-13 weeks

van den Berg, Prenatal Diagnosis 1999: 19
Semin Perinatol 29:312-320
images.main.uab.edu/healthsys/ei_0096.jpg
CVS

Advantages:
- Early detection

Disadvantages
- More technically challenging than amniocentesis
- Risk of cross contamination/incorrect sampling of up to 4%

Semin Perinatol 2005: 29:312-320
CVS

Accuracy:
• Appears to be accurate for diagnosis
• Some risk of indeterminate results from placental mosaicism

Risks:
• Loss rates in twins reported range from 0-4.5%
• Recent studies on CVS and multiples: loss rates for CVS no different than amniocentesis

Prenat Diagn 19:234-244, 1999
Semin Perinatol 29:312-320
Amniocentesis

- Transabdominal removal of amniotic fluid for genetic analysis
- 15-20 weeks

van den Berg, Prenatal Diagnosis 1999: 19
Amniocentesis in multiples

• First described in twins in 1980
  – Described sampling clear fluid from first sac then adding indigo carmine
  – Sampling of clear fluid from the second sac ensured adequate sampling from both

• Technique still useful with mono- or dichorionic twins, high-order multiples

• Mapping is key
Use of marker dye

• Methylene blue
  – Fetal hemolysis
  – Methemoglobinemia
  – Multiple ileal obstruction
  – Jejunal atresia

• Indigo carmine
  – Not associated with abnormal fetal outcomes
Amniocentesis in multiples

• Loss rates in twins:
  – Range from 2.5-3.5% following genetic amniocentesis

• Monochorionic twins
  – Sample one or both?

Semin Perinatol 2005 29:312-320
New Microarray technology

  - 300 cases
  - Array comparative genomic hybridization
  - Smaller deletions or duplications seen
  - 58 copy number variations found
    - 2 clinically significant

Van den Veyver, Prenat Diag (2008), pub online 14 Nov 2008
Microarray- pitfalls

• Case reports of monochorionic (and monozygotic) twins with differing microdeletion sizes as detected by microarray
• Different phenotypes CAN be seen
• Microdeletions does not ALWAYS equal clinical syndrome
PRACTICAL ISSUES: ANTENATAL CARE
Maternal nutrition & weight gain

Goals:
1. Optimize fetal growth
2. Reduce the incidence of obstetrical complications
3. Minimize risk preterm birth
4. Avoid excess weight gain
### Recommended rate of maternal weight gain for twins

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Underweight</th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (&lt;20 wk)</td>
<td>1.25-1.75 lb/wk</td>
<td>1-1.5 lb/wk</td>
<td>1-1.25 lb/wk</td>
<td>0.75-1 lb/wk</td>
</tr>
<tr>
<td>Mid (21-28 wk)</td>
<td>1.5-1.75 lb/wk</td>
<td>1.25-1.75 lb/wk</td>
<td>1-1.5 lb/wk</td>
<td>0.75-1.25 lb/wk</td>
</tr>
<tr>
<td>Late (&gt;28 wk)</td>
<td>1.25 lb/wk</td>
<td>1 lb/wk</td>
<td>1 lb/wk</td>
<td>0.75 lb/wk</td>
</tr>
</tbody>
</table>

Institute of Medicine weight gain guidelines

<table>
<thead>
<tr>
<th>Prepregnancy BMI</th>
<th>BMI</th>
<th>Singleton- total gain (lb)</th>
<th>Twins- total gain (lb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>underweight</td>
<td>&lt;18.5</td>
<td>28-40</td>
<td>None made</td>
</tr>
<tr>
<td>normal</td>
<td>18.5 – 24.9</td>
<td>25-25</td>
<td>37-54</td>
</tr>
<tr>
<td>overweight</td>
<td>25.0 – 29.9</td>
<td>15-25</td>
<td>31-50</td>
</tr>
<tr>
<td>obese</td>
<td>&gt;30</td>
<td>11-20</td>
<td>25-42</td>
</tr>
</tbody>
</table>

ANTENATAL TESTING
Surveillance for Fetal Well-Being

• Estimated fetal weight

• Amniotic fluid assessment
  – Subjective assessment
  – Maximum vertical pocket

• Umbilical cord Doppler velocimetry
  – Only if underlying indication of FGR
Ultrasound Surveillance

Monochorionic twins
  – Ultrasound evaluation every 2 weeks beginning in the 2nd trimester
    • Abnormal growth
    • Amniotic fluid discordance

Dichorionic twins
  – Ultrasound every 4 - 6 weeks after 20 weeks gestation
    • Optimal detection of fetal growth deceleration between 20 and 28 weeks of gestation

Cervical length measurement up to 26-28 weeks
Surveillance for Fetal Well-Being: High Risk

• FGR, discordant growth, abnormal amniotic fluid volume, monoamnionicity, preeclampsia

• Uncomplicated MC/DA twins also at increased risk of in-utero death

• Consider antenatal testing twice a week

• Growth every 2-3 weeks
Surveillance for Fetal Well-Being: Low-Risk

- Routine use of antepartum testing in uncomplicated DC twins has been demonstrated to be beneficial in retrospective but not prospective studies.

- NSTs or BPPs performed once or twice weekly may identify those fetuses that would benefit from early delivery:
  - ~32 wks MC twins
  - ~34-36 wks DC twins
What is discordant growth?

Weight larger twin – weight smaller twin

Weight larger twin

15-25%
TIMING OF DELIVERY
When should uncomplicated monochorionic twins be delivered?
“Postdates” Pregnancy in Twins

- Prospective risk of fetal & neonatal death intersects ~ 38 -39 weeks in twins (Kahn et al, ObGyn 2003;102)
“Postdates” Pregnancy in Twins

• Prospective risk of fetal & neonatal death intersects ~ 38 -39 weeks in twins (Kahn et al, ObGyn 2003;102)

• Study of multiple gestations (99.8% twins) risk of fetal & neonatal death were equivalent at 37 – 38 weeks (Sairam S et al, ObGyn 2002;100)

• Take home point: deliver at 38 weeks
The problem: these data do not address chorionicity!
Studies arguing for early delivery

Trial 1
• 1000 twins (20% MC, 80% DC)
• MC twins: higher stillbirth rates than the DC twins (3.6% vs. 1.1%; \( P = .004 \))

Trial 2
• A retrospective analysis from the United Kingdom
• 151 uncomplicated monochorionic pregnancies
• Risk for unexpected stillbirth after 32 weeks was 4.3% (1 in 23)

Lee at al, Obstet Gynecol, 2008
Study arguing for later delivery

Breathnach, Obstet Gynecol, 2012:
• Prospective ESPIRiT study, Twins, Ireland
• N = 1001 pregnancies (20 % MC, 80% DC)
• Prospective risk fetal death:
  – 1.5% after 34 weeks for MC,
• Compositive morbidity: 41% at 34 weeks vs 5% at 37 weeks.
• Consider delivery at 37 weeks for MC.
Take home: delivery for monochorionic twins

Delivery of uncomplicated monochorionic, diamniotic twins - between 34 and 38 weeks

More research desperately needed!
SUMMARY OF RECOMMENDATIONS

DIAGNOSIS- chorionicity matters!
NUTRITION- follow weight gain goals
REFERRAL TO MFM- for any high risk developments

ANTENATAL TESTING
  – Q 2 week screen for TTTS
  – Monthly growth
  – Twice weekly antenatal at 32-34 weeks

DELIVERY- between 34-38 weeks if uncomplicated
Thank you!