Invasive Prenatal Diagnosis

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BACKGROUND

- The prevalence of chromosome abnormalities in clinically recognized early pregnancy loss is greater than 50%
- Fetuses with aneuploidy account for 6-11% of all stillborns and neonatal deaths
- Risk of aneuploidy increases with abnormalities involving a major organ or two or more minor structural abnormalities
STRATEGIES AVAILABLE TO SCREEN FOR CHROMOSOME ABNORMALITIES

- Combining maternal age with a variety of 1st and 2nd trimester ultrasound and biochemical markers that include:
  - NT measurement
  - PAPP-A, HCG, AFP, estriol, and inhibin levels
- Provide an adjusted risk for trisomy 21, 18, and 13
- Do not exclude the possibility of an affected fetus
AMNIOCENTESIS

• Offered between 15-20 weeks of gestation
• All of the large collaborative studies evaluating risk were performed before the use of high-resolution concurrent ultrasound
• More recent studies have suggested a miscarriage rate as low as 1 in 300-500 and may be even lower in experienced hands
COMPLICATIONS FROM AMNIOCENTESIS

- Transient vaginal spotting or amniotic fluid leakage – 1-2% of all cases
- Chorioamnionitis - <1 in 1000 cases
- Perinatal survival after amniotic fluid leakage is > 90%
- Needle injuries reported but very rare
- Culture failure occurs in 0.1% of samples
AMNIOCENTESIS SUCCESS

- The incidence of pregnancy loss, blood contaminated specimens, leaking of amniotic fluid, and the need for more than one puncture are related to:
  - operator experience
  - small gauge needles (22 gauge)
  - ultrasound guidance
EARLY AMNIOCENTESIS

- Performed between 11-13 weeks
- Higher rate of pregnancy loss and complications than mid-trimester amnio
- Loss rate 2.5%
- Higher rate of talipes (club foot) – 1.4%
- Higher rate of membrane rupture
- Higher rate of amniotic fluid culture failures
- EARLY AMNIO SHOULD NOT BE PERFORMED (<14 WEEKS GESTATION)
CHORIONIC VILLUS SAMPLING

- Performed after 9 completed weeks gestation
- May be performed transcervically or transabdominally with no difference in loss rate
- Primary advantage of CVS over amniocentesis is that results are available earlier in pregnancy
- Available for abnormal first trimester screening results
The overall pregnancy loss rate after CVS is greater than the rate after midtrimester amnio due to the increased background rate of spontaneous pregnancy loss between 7-16 weeks.

Recent data suggest that the loss rate for CVS appears to approach and may be the same as for amnio.
CVS AND LIMB REDUCTION DEFECTS

• Analysis by World Health Organization (WHO) found an incidence after CVS that was not significantly different than the incidence in the general population
• May be higher if performed before 9 weeks gestation
COMPLICATIONS AFTER CVS

- Vaginal spotting or bleeding – up to 32% after transcervical CVS, less after rate of transabdominal CVS
- culture failure, amniotic fluid leakage, or infection is less than 0.5%
CORDOCENTESIS

- Procedure-related pregnancy loss rate reported to be less than 2%
- Rarely is needed but may be useful to further evaluate chromosomal mosaicism discovered after amniocentesis or CVS
INCREASED RISK FOR ANEUPLOIDY

- Increased maternal age
- Previous fetus or child with aneuploidy
- Structural abnormalities identified by ultrasound
- Parental carrier of chromosomal translation or inversion
- Parental aneuploidy or mosaicism for aneuploidy
ASSESSING THE RISK FOR ANEUPLOIDY

- Refer to maternal age-specific aneuploidy risk tables
- Use adjusted risks after first or second trimester screening
- Helpful to compare the patient’s individual risk with the risk cut-off used to indicate a positive screening test result
WHO SHOULD HAVE PRENATAL DIAGNOSIS FOR FETAL CHROMOSOME ABNORMALITIES?

• Maternal age of 35 years alone should no longer be used as a threshold to determine who is offered screening vs. who is offered invasive testing (ACOG)

• Based on many factors, including the age related risk of aneuploidy, the risk of pregnancy loss from the procedure and the personal consequences of having an affected child
LABORATORY TESTING FOR ANEUPOLOIDY

- Metaphase analysis of cultured amniocytes (7-10 days) or chorionic villus cells is the preferred method (1-2 days)
- Fluorescence in situ hybridization (FISH) provides rapid results for specific chromosome abnormalities (13, 18, 21, X, and Y)
CHROMOSOME MOSAICISM

- Definition: the presence of more than one cell line identified during cytogenetic analysis
- Occurs in 0.25% of amnio specimens and 1% of CVS specimens
CHROMOSOMAL MOSAICISM

• If found by CVS, amnio is typically performed to assess whether mosaicism is present in amniocytes
• Most cases reveal normal amnio results signifying that mosaicism is confined to the trophoblast
• Some cases associated with IUGR
INVASIVE DIAGNOSIS IN WOMEN WITH CHRONIC INFECTIONS

- No apparent increased risk of neonatal infection in women with hepatitis B or hepatitis C who underwent amniocentesis (but small study numbers)
- Insufficient data re CVS
- Amniocentesis in women with HIV has been shown to increase vertical transmission rate in women not receiving retroviral therapy; does not appear to increase neonatal infection in women receiving retroviral therapy
- Discuss noninvasive screening options in these patients
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
- 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%))
COUNSELING AFTER DIAGNOSIS OF A CHROMOSOMAL ABNORMALITY

• Patient should receive detailed information of individuals with the specific chromosomal abnormality
• Can refer to genetic counselor and/or clinical geneticist
INFORMATION AFTER DIAGNOSIS OF ANEUPLOIDY

- Possibly referral to pediatric specialists, support groups, social workers, or clergy
- Discuss option of pregnancy termination
INVASIVE TESTING IN A PATIENT WHO WOULD NOT TERMINATE?

- Can provide useful information for the patient and physician
- If a chromosomal abnormality is found, it may help the physician and family develop a management plan for the remainder of pregnancy, labor, delivery, and neonatal period
- A normal result often provides significant patient reassurance
- Some patients change their minds with an abnormal reading
CONCLUSIONS

• Amniocentesis has a lower than previously thought loss rate
• CVS loss rates approach amnio in experienced individuals and centers
• Early amnio should not be performed
CONCLUSIONS

Invasive diagnostic testing for aneuploidy should be available to all women regardless of maternal age and regardless if a patient would terminate an abnormal pregnancy.
CONCLUSIONS

• Patients with an increased risk of fetal aneuploidy include women 35 years old and above, women with a previous child or fetus with aneuploidy, one major or at least two minor fetal structural abnormalities identified by ultrasound, parental translocation or inversion, or parental aneuploidy