PRENATAL GENETIC DIAGNOSIS

Indications for prenatal diagnosis

- Advanced maternal age
- Positive maternal serum alpha fetal protein
- Balanced maternal or paternal translocation
- Risk for detectable Mendelian disorder
- Family history of neural tube defects
- Abnormal fetal ultrasonography
- History of fetal wastage
- Parental concern

Alpha Fetal Protein

- Glycoprotein MW 70,000 Dalton
- Produced by yolk sac and liver at 4-8 weeks
- Liver later becomes dominant source
- Most MSAFP gets to mother by diffusion
- Transmembranous transport from AF is 6%
- Any increase in production (twins) or increase in AF (NTD) leads to increase
- Expressed as multiples of the median (MOM) for given GA
- Maternal race, weight, multiple pregnancy, IDDM
- Each lab must establish norms and risks
  - Diabetics have overall increased risk for anomalies
  - AA have higher AFP at any given GA
  - FH impacts risk as well
  - Concentrated in very thin, diluted in very obese
- Elevated for α-fetal protein & acetylcholinesterase
- MSAFP is also expressed as MoM for normal pregnancies of same gestational age
- Using 2.5 MoM we can detect 93-96% of open spina-bifida and 100% of anencephalics
- False positives are high (contamination of AF by fetal blood – especially if placenta is crossed by needle)
- AChE is so large that it is not in fetal urine. It will detect 99% of open spina-bifida

Other causes of elevated AFP

- Abdominal wall defects
- Renal agenesis
- Fetal demise or impending demise
- Teratoma
- Congenital nephrosis
- Congenital diaphragmatic hernia
- Some maternal tumors
- IBD in mother
- Feto-maternal hemorrhage
- Oligohydramnios
- Fetal growth restriction

Incidence of chromosomal abnormalities by age

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Sonography

- All women had been encouraged to have amniocentesis if at risk in past years
- Modern sonography will detect virtually all lesions
- Gestational age errors, multiple gestation, fetal demise are all detectable
- Normal U/S allows 90% reduction in risk for NTD based on α-fetal protein
- Early genetic sonography is highly sensitive and statistically superior to later ultrasonography for Down syndrome detection.
- Early midtrimester sonography achieves a diagnostic accuracy similar to that currently reported for first-trimester nuchal translucency.

Triple Screen

- A Fetal Protein (AFP)
- Human chorionic Gonadotropin (hCG)
- Unconjugated estriol (μE3)
- Estimate risk of fetus with trisomy 18 and trisomy 21
- Low AFP, hCG and μE3 → trisomy 18
- Low AFP, μE3 and high hCG → trisomy 21
- Biologic basis for this unknown
- Three specific adjustments
    - Maternal weight
        - Obese women have lower MASAFP – dilution
    - Diabetes Mellitus
        - IDDM have AFP that is 2/3 that of non-diabetic
    - Race
        - AA women have AFP 9-15% higher
    - Smoking ????
        - Have lower incidence of trisomy 21 !!!!!

First Trimester Screening

- Now an option for pregnant women if certain criteria are met
- Nuchal translucency (NT), have allowed for earlier, noninvasive screening for chromosomal abnormalities and, when combined with serum screening in the first trimester, have comparable detection rates as standard second-trimester screening
- Low serum AFP (31% of trisomies)
- Free beta-hCG reduced in aneupoidy
- Schwangerschafts protein 1 (SP1) also known as pregnancy specific beta-1 glycoprotein - median for abnormal group (trisomy 18 and 21) is ½ that of normal group

Quadruple Screen

- AFP, estriol, Hcg, Inhibin

Inhibin in combination with alpha fetal protein

- The best three-analyte combination was maternal serum -fetoprotein, free -human chorionic gonadotropin, and dimeric inhibin A
- 97% of Down syndrome cases were detected at a false-positive rate of 16%.
- At a slightly higher false-positive rate (18%) maternal serum -fetoprotein, estriol, and intact human chorionic gonadotropin detected only 79% of cases.
- 67% (37/55) detection was obtained with use of the 2-analyte combination of a-fetoprotein and dimeric inhibin A

Nuchal Translucency

- Higher rates of nuchal translucency screening were associated with lower rates of chorionic villus sampling and invasive testing.
- The addition of first-trimester screening may lead to reduced rates of invasive testing and fewer losses of normal pregnancies.
- The use of nuchal translucency adds to the sensitivity of detection but can add as much as $300,000 in cost for each detected Down's syndrome baby.
- Increased nuchal skin alone, in the absence of other ultrasonographic dysmorphologic features, does not generally help to identify fetuses with other abnormal karyotypes.
- The nuchal thickness/humerus length ratio and maternal age had a 79.8% detection rate at a 22.1% false-positive rate, compared with maternal age plus humerus length (sensitivity, 55.1%) or maternal age plus nuchal thickness (sensitivity, 66.7%) at the same false-positive rate. For women >35 years old the values were 80% and 22.0%, respectively.
- Nuchal thickness, humerus length, and maternal urine β-core fragment levels are another sensitive assay from Down's syndrome
- Normal nuchal thickness in the midtrimester indicates reduced risk of Down syndrome in pregnancies with abnormal triple-screen results
- Midtrimester nuchal thickness measurement significantly detected postnatally confirmed CHD in chromosomally normal fetuses.

PAPP

- First-trimester free -human chorionic gonadotropin and pregnancy-associated plasma protein A screening for Down syndrome can achieve detection rates as high as those associated with –alpha-fetoprotein and human chorionic gonadotropin or alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol screening in the second trimester.
- Liklihood ratios for detection of various abnormalities with given tests

TEST	DOWN SYNDROME	UNAFFECTED
No test	1.0	1.00
NT alone	4.9	0.28
PAPP-A, fbhCG	10.6	0.15
NT, PAPP-A, fbhCG	36.1	0.08
AFP, uE3, hCG (triple test)	8.4	0.13
AFP, uE3, hCG, INH-A (quad test)	14.0	0.08
All 7 tests	260.9	0.02

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Screening Strategies

- Triple screen: maternal age and midtrimester serum alpha-fetoprotein, human chorionic gonadotropin (hCG), and unconjugated estriol
- Quad screen: triple screen plus serum dimeric inhibin A
- First trimester screen: maternal age, serum pregnancy-associated plasma protein A and free b-hCG and fetal nuchal translucency at 10 to 14 weeks' gestation
- Integrated screen: first-trimester screen plus quad screen, but first-trimester results are withheld until the quad screen is completed when a composite result is provided
- Sequential screen: first-trimester screen plus quad screen, but the first-trimester screen results are provided immediately and prenatal diagnosis offered if positive
- Combined first-trimester screening for fetal Down syndrome is more cost-effective than universal second-trimester triple serum screening.

Chorionic Villus Sampling (CVS)

- 1991 – 5/289 pregnancies who had transabdominal CVS at 8 to 9.5 weeks
- Background incidence 5.42/10,000
- In a study of over 80,000 CVS the rate was 6.0/10,000
- Decreased perfusion, embolization
- Should be done at 9-12 weeks
- At least 200-250 yield "*experience*"
- Reserved for women "at risk "
- Fetal loss had been 1:200 (.5%)
- Age of 35 chosen
- Loss now considered to be 1:400 or even lower
- Maternal screening and u/s are so good that only those with abnormal findings need have amniocentesis
- Costs
- Pregnancy loss
- Transvaginal fluid leakage
- Bleeding
- Fetal trauma
- Difficulty in obtaining fluid
- Uterine contraction
- Membrane tenting
- Fetal movement and pocket obliteration
- Bloody fluid
- Mislabeling

Other Technologies

- PUBS
- Fetal tissue sampling
    - Liver
    - Muscle
    - Skin
- Fetal Cells in Maternal Blood
- Fetal Cells Vaginal Fluid

FUNDAMENTAL QUESTIONS

1. What is AFP and from where does it arise?
2. How does it get into the maternal circulation?
3. In what conditions is it elevated and why?
4. In what conditions is it reduced?
5. Describe the rate of rise of chromosomal trisomies with advancing gestational age?
6. How is an amniocentesis performed?
7. When and how do neural tube defects occur?
8. What conditions are commonly diagnosed by amniocentesis?
9. What are the risks of amniocentesis?
10. What methods are available for first trimester prenatal diagnosis?
11. What is PAPP?
12. What is the role of inhibin?
13. What ultrasonographic findings are seen in trisomy 21 in the first and second trimester?
14. What are the risk of amniocentesis? CVS?
15. What is CVS, how is it performed, what can be diagnosed?
16. What are the risks of CVS?
17. List five screening strategies and the benefits of each?