Fetal pathology with elevated maternal serum alpha-fetoprotein

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Learning objectives:

At the conclusion of the presentation, learners will be able to:
- recognize usefulness of alpha-fetoprotein as a clinical test
- describe fetal presentation of different forms of open neural tube defect
- identify other clinico-pathologic aspects of fetal maturation which may manifest with alpha-fetoprotein level changes
- question issues of normal vs abnormal growth, including their ethical considerations.

Case #1 (86-A-8). Female stillborn, 40 weeks and 6 days, delivered after 30 hours of fetal demise.

Fetal weight 2150 gms, length crown to heel 46 cm.

Mother, 24 yo, had cold during early pregnancy (significant enough to report it consistently). Mildly elevated maternal serum alpha-fetoprotein was on record. Previous pregnancy resulted in a healthy child.

The following abnormalities may be derived from altered morphogenesis between 35 and 45 days post conception. Causes probably heterogeneous; possible genetic etiology. Esophageal atresia present, most likely responsible for elevated AFP.
Double-Outlet Right Ventricle with Transposition of the Great Arteries

- Ventricular septal defect
- Pulmonary artery from left ventricle with septal defect override
  Aorta arising from right ventricle
- Obstruction to left-sided outflow from right ventricle (coarctation of the aorta)
- Right ventricular hypertrophy

- Ventricular septal defect
- Aorta arising from left ventricle with septal defect override
  Pulmonary artery from right ventricle
- Obstruction to right ventricular outflow (pulmonary stenosis)
- Right ventricular hypertrophy
ALPHA-FETOPROTEIN

- Protein 70 000 kD, single polypeptide chain of 591 amino acids and a carbohydrate, main fetal protein
- Gene: chromosome 4, q11-22 (family of genes encoding also albumin and vitamin-D binding protein)
- Produced by yolk sac up to 10 weeks, and subsequently by fetal liver
- Maximal concentration in fetal serum at 16 weeks, then decreasing; amniotic fluid parallels that level hundred times lower (3 000 000 vs 20 000 ng/mL)

Elevated maternal:
- Fetal open neural tube defect
- Congenital nephrosis
- Cystic hygroma (Turner’s)
- XII & Esophageal atresia
- Trisomy 13
- Hydrops
- Fetal blood contaminant
- Fetal demise
- Hydrocephalus
- Herpesvirus liver necrosis
- Teratoma, sacrococcyx
- Rh isoimmune disease
- Omphalocele
- Twins, other multiple
- Underestimated age

Low maternal:
- Down’s syndrome
- Fetal demise
- Molar pregnancy
- Trisomy 18
- Pseudocyesis (imaginary pregnancy)
- Spontaneous abortion
- Normal pregnancy
- Overestimated age

**ALPHA-FETOPROTEIN**

- Maternal serum and amniotic fluid AFP are used to detect some serious fetal anomalies
  - Maternal serum elevated in 80 – 95% of cases of fetal open neural tube defect
  - Maternal serum AFP low in about 30% of cases of fetal Down’s syndrome
  - A quad test of AFP, hCG, uE3, inhibin-A, effective in 70-80%.
- AFP in non-pregnant patients:
  - High in 80% of hepatocellular carcinomas
  - High in 50% of germ cell tumors
  - Children: high in 100% with hepatoblastoma

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**Neural Tube Defects**

- By 19 days, cell plate forms for CNS
- Flat plate rolls to form a hollow tube and drops into the embryo under the newly formed skin to finally develop into brain and spinal cord
- Neural tube formation is normally complete 4 weeks after fertilization - failure of fusion leads to permanent developmental defects

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**Neural Tube Defects**

- Incidence 8:1000 Ireland - 1:1000 USA, Japan.
- Folic acid 0.4mg/day 1 month before through 3 months after conception can prevent to 70% of all neural tube defects
- Major types of neural tube defects:
  - Meningomyelocele (spina bifida)
  - Encephalocele
  - Anencephaly
Case #2 (A4474), Meningomyelocele (Spina bifida)

Male, intrauterine death in mid-trimester GA. Length crown to heel 24.5 cm, Fetal weight 283 gms.

Mother, 32 yo, had elevated serum alpha fetoprotein level up to 345.6 ng/ml (7.3 Multiples of Median) at about 17 weeks of gestation. Spina bifida was detected on ultrasound. Previous pregnancy resulted in a healthy child.

Father had been treated with post-surgery chemotherapy for astrocytoma. No maternal or paternal history of congenital abnormalities.
Case #3 (S435/A4451): **Encephalocele**
Female, intrauterine death. Probably 20 weeks (reason for S# vs A#)

Mother 29 yo Caucasian, without congenital or mental abnormalities. First pregnancy. Elevated AFP. Genetic counseling suspected trisomy 13.

Mother's three siblings died in fetal or neonatal stage of development. No paternal history of congenital abnormalities.
Case #3 (A4451/S435). Summary of findings:

1. Holoprosencephaly
   a. Cyclopia
   b. Midline proboscis superiorly to orbital opening, with absence of nasal cavity
   c. Absence of olfactory bulbs and optic nerves
   d. Single lobe cerebrum with absence of interhemispheric fissure
   e. Encephalocele

2. Polydactyly, both upper and lower extremities
Case #4 (87-A-33). Anencephaly
Male stillborn (penis and undescended testicle, but also uterus with fallopian tubes and vagina), 33 weeks, delivered spontaneously.

Fetal weight 950 gms, length crown to heel 23 cm.

Mother, 27 yo AA, negative for sickle cell disease, stated uneventful course. Prenatal care out-of-state. First pregnancy; polyhydramnios dx at delivery.

The following abnormalities are not compatible with life. A cause of defect in neural tube closing is not known.
Case #4 (87-A-33): Anencephaly - Summary of findings:

I. Persistent neural groove (unclosed neural plate)
   A. Anencephaly with amelia, unstructured neural tissue present
   B. Craniospinal rachischisis, with absent cranial vault, reduced number of cervical vertebrae and vertebral spine deformity
   C. Multiple organ abnormalities (absent pituitary, hypoplastic lungs & adrenals, hyperplastic thyroid and thymus)

II. Omphalocoele, with herniation of abdominal contents and short duplication of small bowel

III. Male pseudohermaphroditism, with testis and uterus

IV. Placental pathology (bivascular umbilical cord)

Case #5: This is a case of the successful near-term extrauterine abdominal pregnancy

- Mother 26 yo, elevated serum alpha-fetoprotein: 3.08 MoM @ 18 weeks & 3.21 MoM @ 22 weeks; declined amniocentesis.
- Cesarean Section at 37 weeks of gestation due to diffuse abdominal pain
- Healthy normally-developed male infant: 3255 gm and 51 cm crown-heel
- Characteristic placental morphology
Case #5: Summary of placental findings:
Subperitoneal placenta accreta succenturiate
in the case of a successful near-term extrauterine abdominal pregnancy

- Placenta 772 gm
- accreta: no decidua
- succenturiate: multilobar due to uneven blood supply
- trophoblastic partial remodeling of maternal arteries
- supportive dilated maternal veins, non-infiltrated
- Trivascular umbilical cord 25 cm, membranous insertion