Biochemical Changes in Pregnancy and Prenatal Diagnosis

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Introduction

• Pregnancy is a physiological state with alteration in general body system. There are;
• Changes in metabolism
• Changes in function of digestive system
• Changes in renal function
• Changes in weight
• Changes in water and blood volume
• Changes in cardiovascular system

NB: The above changes are induced by the biochemical change - hormone change.
Cont’d

- Weight gain about 12kg from maternal fluid retention, fat store and product of conception.
- Many plasma constituent are influenced by sex hormones e.g. plasma urate and iron.
- Increase in carrier protein in proportional to substance bound to them e.g. plasma thyroxine.
- Progressive haemodilution which causes reduction of albumin and calcium.
- Renal glycosuria; increase in GFR by about 50%.
Sequential hormonal changes during menstrual cycle

1. degeneration of corpus luteum →↓ estrogen, ↓ progesterone, ↓ inhibin →↑ FSH & LH
2. follicles develop →↑ estrogen levels
3. plasma estrogen levels increase
4. ~day 7, dominant follicle secretes high levels of estrogen
5. plasma estrogen level increases sharply
6. high estrogen levels suppress FSH levels causing degeneration of non-dominant follicles
7/8. ↑↑ estrogen levels →↑ LH surge (positive feedback)
9. 1st meiotic division of 1° oocyte
10. ~day 14, ovulation occurs
11. the dominant follicle collapses, and reorganizes as the corpus luteum
12. corpus luteum secretes estrogen & progesterone
13. plasma levels of estrogen & progesterone increase, suppressing release of GnRH, LH, & FSH
14. ~day 25, corpus luteum spontaneously degenerates
15. ↓ secretion & plasma levels of estrogen & progesterone
16. ↓ estrogen & progesterone → ↑ FSH & LH levels which begin follicular development of the next menstrual cycle
Follicular life cycle through menstrual cycle

**Follicular phase**
- BLEEDING STARTS
- Multiple follicles develop
- One follicle becomes dominant
- Dominant follicle matures
- Ovulation occurs

**Luteal phase**
- Corpus luteum functions
- Corpus luteum degenerates
Endometrial changes during menstrual cycle

Endometrial thickness

Day

1 5 10 15 20 25 28 5

Uterine phase

Menstrual Proliferative Secretory Menstrual

Ovarian phase

Follicular Luteal

Ovarian event

Estrogen

Progesterone Estrogen

Ovulation

fig 17-22
Hormonal interactions in the female
Hormonal initiation of ovulation

1. **Hypothalamus** Secretes GnRH
   - ↑GnRH (in hypothalamo-pituitary portal vessels)

2. **Anterior pituitary** Secretes LH
   - LH surge

3. **Ovary**
   - Large amounts of estrogen
   - Corpus luteum
   - Progesterone and estrogen

**Begin**
Endocrine changes:

• Prolactine concentration increases markedly but act after delivery.
• Human growth hormone is suppressed.
• Insulin resistance develop.
• Thyroid function changes little.
• Trans placental calcium transport is enhanced.
• Corticosteroid concentration increased.
• Aldosterone concentration increased.
• Angiotensin and renin increased.
Specific hormonal changes

Hormones produced by the placenta

- 1. oestrogen
- 2. progesteron
- 3. Human chorionic gonadotrophins (hCG)
- 4. peptide hormones: mainly placental lactogen and growth hormone.
Human chorionic gonadotrophin (hCG)

- Fertilization of the ovum prevents the regression of the corpus luteum.
- Instead, the corpus luteum enlarges, stimulated by the glycoprotein hormone, hCG, produced by the trophoblast (the developing placenta).
- This hormone (assays usually measure the B-subunit) can be detected in maternal blood 6-9 days after conception and may be detectable in the urine 1-2 days later.
- Its detection in the urine provides a highly sensitive and specific test for the diagnosis of pregnancy.
- The secretion of B-hCG begins to fall by 10-12 weeks, although it remains detectable in the urine throughout pregnancy.
- hCG is also produced by some tumours.
Cont’d

• hCG is considered to play a role in the early pregnancy discomforts like morning sickness and fatigue.
• hCG in the early days of pregnancy helps to support the pregnancy by stimulating the ovaries to produce progesterone,
• resulting in the cessation of the menstrual cycle during pregnancy.
• Stimulate production of testosterone in male
• Test positive in plasma or urine 1 or 2 weeks after the first missed period
• More sensitive immunoassay techniques may detect plasma level much earlier especially in ectopic pregnancy
• Its peaks at 7 to 9 weeks
• Should double every 2 days in normal pregnancy
• Falls rapidly to lowest level at abt 16 wks
Cont’d

• hCG levels are high in
•  -Multiple pregnancies
•  -Rh isoimmunization
•  -Hydatidiform mole and chorionic carcinoma
•  -Diabetis mellitus in pregnancy
•  It is a glycoprotein with similar structure to TSH, LH and FSH
Oestrogens

• The stimulated corpus luteum secretes large amounts of oestrogens and progesterone,
• But after 6 weeks the placenta and Foetus becomes the major source of these hormones.
• Stimulates the womb to prepare for receiving a fertilized egg.
• Stimulates the breasts to develop milk glands and the nipples to enlarge to prepare for breastfeeding.
• For maintenance of pregnancy during the development and maturation of the foetus
• Stimulate production of phospholipids and synthesis of prostaglandins
• Most oestriol found in urine is from foetus and highest at parturition.
• Urine level is low in anaencephaly or in placental failure.
• While levels of estrogen are high in a woman’s body during pregnancy, the levels fall dramatically after childbirth.
• Typical changes in the excretion of pregnanediol (the main urinary metabolite of progesterone), oestriol and hCG are shown in the next figure.
Typical changes in the excretion of oestriol, pregnanediol and hCH in maternal urine during pregnancy.
Progesterone

- Progesterone is produced in a woman’s ovaries and in the placenta of a pregnant woman.
- During the menstrual cycle progesterone stimulates the uterine lining to thicken in anticipation of receiving a fertilized ovum.
- Progesterone during pregnancy assists placental functioning, and inhibits uterine contractions that could result in miscarriage.
- Progesterone also influences other processes during pregnancy such as temperature regulation, breast milk production and blood vessel dilation.
- The amount of progesterone in the body increases over time during pregnancy and can relax not only the muscles in the uterus, but other smooth muscles in the body like the muscles of the bladder, bowels and esophagus;
- resulting in conditions like heartburn and constipation.
- Cartilage in the body is also affected by progesterone production during pregnancy.
- The hormone softens the cartilage and can result in pain in the pubic bone.

NB: A low serum progesterone early in pregnancy suggests poor luteal function and is seen in about a third of women with recurrent abortion.
Human placental lactogen (hPL)

• It is secreted by syncytotrophoblast
• Detected after about the eighth week of gestation.
• It is level increase when the level of HCG start to drop.
• HPL has no effect on fetus.
• Secreted into maternal serum to mobilise glucose and fatty acids for the nourishment of the foetus.
Cont’d

• Stimulate protein synthesis at cellular level.
• Carbohydrate: stimulate insulin secretion and inhibit insulin action.
• Fat: mobilize fat from body store (lipolysis) lead to increase maternal blood glucose and maternal tissue can not utilize the glucose so the glucose will be available for fetus.
• The breast:
  o mammary growth during pregnancy.
  o produce of colostrums and milk production
• Used to assess threatened miscarriage and monitor late pregnancy.
Oxytocin

• The pituitary gland secretes this hormone in the brain.
• Activates Braxton Hicks contractions as well as labour contractions.
• It is also responsible for stimulating the milk glands to produce milk, the milk ejection reflex.
• A synthetic version of this hormone, Pitocin, is sometimes used to induce labour contractions.
• Oxytocin is sometimes referred to as the cuddle hormone, as it can be released in response to pleasurable contact with your baby, your partner, and during sex.
Melanocyte

• This hormone causes pigmentation changes in the mother’s body which may be seen as linea nigra, cholasma, and darkened nipples during pregnancy.

• The pigmentation changes usually fade after childbirth.
Thyroxine

- Produced in the thyroid gland with stimulation from the adeno-hypophysis
- Thyroid enlargement with a 20% increase in function (from tissue hyperplasia and increased vascularity)
- T3 decreases until the end of the first trimester, then stabilizes and return to normal 12-13 weeks postpartum
- T4 increases during pregnancy
- BMR increased 25% resulting from metabolic activity of the feto-placental unit
- Protein bound iodine (PBI) increases from 3.6-8.8 to 10-12 units/dl during pregnancy
- Palpitations, tachycardia, emotional lability, heat intolerance, fatigue, perspiration
- May be involved with severe nausea and vomiting of pregnancy
Relaxin and Endorphins

Relaxin
- The function of relaxin during pregnancy is to
  - soften and lengthen ligaments and tissue to allow for easier passage of the baby through the birth canal.

Endorphins
- The body produces endorphins in response to pain or stress, and pregnancy is no exception.
- They will be produced throughout pregnancy, especially during childbirth. Levels of endorphins will drop after delivering the baby.
Hormones in foetus

• Secrete most of its hormones by 12wks of gestation which are;
  • - growth hormones is detected about 12wks
  • -prolactin
  • -arginine vasopressin
  • -oxytocin
  • -TRH
  • -TSH, T3 and T4
  • -GnRH, LH and FSH
• -Foetal adrenal glands secrete larger quantities of DHEAS than adult.
<table>
<thead>
<tr>
<th>Analytes</th>
<th>Normal (non-pregnant)</th>
<th>Pregnancy</th>
<th>Abnormalities and possible interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>11.5–16.5</td>
<td>11.0–15.0</td>
<td>Abnormal results need to be considered in conjunction with the patient’s clinical state</td>
</tr>
<tr>
<td>White cell count (x 10^6 per mL)</td>
<td>4.0–11.0</td>
<td>Unchanged</td>
<td></td>
</tr>
<tr>
<td>Platelets (x 10^6 per mL)</td>
<td>150–450</td>
<td>Unchanged</td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>135–145</td>
<td>132–140</td>
<td>Abnormal results need to be considered in conjunction with the patient’s clinical state</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.5–5.5</td>
<td>3.2–4.6</td>
<td>↑ in: dehydration</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>2.5–6.8</td>
<td>1.0–3.8</td>
<td>↑ in: dehydration hyperemesis gravidarum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>late stages of pre-eclampsia</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>0.06–0.1</td>
<td>0.04–0.08</td>
<td>↑ in: renal impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>late stages of pre-eclampsia</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>3.0–5.4</td>
<td>3.0–5.0</td>
<td>↑ in: gestational diabetes mellitus (refer to reference 3 for diagnostic criteria)</td>
</tr>
<tr>
<td>Total calcium (mmol/L)</td>
<td>2.2–2.60</td>
<td>2.0–2.40</td>
<td>↑ in: primary hyperparathyroidism</td>
</tr>
<tr>
<td>Ionized calcium (mmol/L)</td>
<td>1.16–1.30</td>
<td>1.16–1.30</td>
<td></td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>0.6–1.0</td>
<td>0.6–0.8</td>
<td>↓ in: vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hyperemesis gravidarum</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>33–41</td>
<td>24–31</td>
<td>↓ in: malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>recurrent vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hyperemesis gravidarum</td>
</tr>
<tr>
<td>Test</td>
<td>Normal Range</td>
<td>High Normal Range</td>
<td>Conditions</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bilirubin (micromol/L)</td>
<td>3–22</td>
<td>3–14</td>
<td>↑ in: intrahepatic cholestasis of pregnancy, HELLP, late stages of pre-eclampsia, acute fatty liver, viral hepatitides</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>1–40</td>
<td>1–30</td>
<td>↑ in: intrahepatic cholestasis of pregnancy, HELLP, late stages of pre-eclampsia, acute fatty liver, viral hepatitides</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>1–30</td>
<td>1–21</td>
<td>↑ in: intrahepatic cholestasis of pregnancy, HELLP, late stages of pre-eclampsia, acute fatty liver, viral hepatitides</td>
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<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>25–100</td>
<td>125–250</td>
<td>↑ in: metabolic bone disorders but placental serum alkaline phosphatase needs to be excluded</td>
</tr>
</tbody>
</table>

↑ increased concentration
↓ decreased concentration

**HELP** — Haemolysis-Elevated Liver enzymes-Low Platelets

* Each laboratory, where practicable, should develop its own reference ranges for pregnant women. Care should be exercised in comparing results from different laboratories due to differences in assay methodologies.

Adapted from reference 7
<table>
<thead>
<tr>
<th>Test</th>
<th>Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total T4</td>
<td>Increased</td>
<td>Increased TBG, Free T4 usually normal</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Increased</td>
<td>Increased transcortin, Free cortisol usually normal</td>
</tr>
<tr>
<td>Transferin or TIBC</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>Increased</td>
<td>Increased caeruloplasmin</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Increased</td>
<td>Placental isoenzyme</td>
</tr>
<tr>
<td>Total protein and albumin</td>
<td>Decreased</td>
<td>Dilution by fluid retention</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Decreased due to increased GFR</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td></td>
<td>Anabolism due to fetal growth and increased GFR</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Raised</td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>Raised</td>
<td></td>
</tr>
<tr>
<td>Oestrogen</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>test</td>
<td>effect</td>
<td>comment</td>
</tr>
<tr>
<td>------------</td>
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<td>--------------------------------------</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>LH and FSH</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Pco2</td>
<td>Decreased due to mild hyperventilation</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>May increase in gestational diabetes</td>
<td></td>
</tr>
<tr>
<td>Urate</td>
<td>Decreased but may be increased if hypertension</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>Glycosuria</td>
<td>Reduced renal threshold</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>May be associated with hypertension</td>
<td></td>
</tr>
</tbody>
</table>
Prenatal Diagnosis
Definition

- Prenatal screening is the systematic application of a non invasive test to identify fetuses at risk for a disease or
- a condition before birth to warrant further invasive investigation or
- direct preventive action.
- It aims at detection of birth defects such as chromosome abnormalities, genetic diseases and other conditions.
Cont’d

• Screening can only evaluate risk of a condition but it cannot determine 100% if the fetus has such condition

• The commonest screening method for fetal abnormalities involves the assessment of a combination of factors: maternal age, second trimester serum markers and second trimester genetic sonogram
• Prenatal screening and prenatal diagnosis have three main purposes;
   i. It aims at enabling appropriate medical or surgical treatment of a condition before or after birth;
   ii. It aims at giving the parents the chance to abort a fetus with the diagnosed condition and
   iii. Giving parents the chance to "prepare" for a baby with a health problem or disability, or the likelihood of childbirth.
Prenatal Diagnosis

• Using a wide variety of screening and diagnostic tests to assess health of a fetus to:
  – Manage the pregnancy
  – Determine potential outcomes
  – Plan for complications at birth
  – Decide whether to continue the pregnancy
  – Discover conditions that may impact future pregnancies
Goals of Prenatal Diagnosis and Counseling

- Assess pregnancy
- Determine specific risks to fetus
- Evaluate prenatal diagnostic options
- Diagnosis fetus when desired and possible
- Educate family about diagnosis, likely outcomes, potential and management options
- Discuss risks, benefits, and uncertainties
- Explore family concerns
- Provide risk assessment for other family members
- Provide psychosocial support and follow-up
Who benefits from prenatal diagnosis?

- Older women (≥ 35) at increased risk of chromosome disorders
- Individuals in populations at increased risk of a genetic disease:
  - Tay-Sachs: Ashkenazi Jews, French Canadians
  - Sickle cell anemia: Africans, Mediterraneans, Arabs, Turks, Indo-Pakistanis
  - Thalassemias: Mediterraneans, Arabs, Turks, Indo-Pakistanis, Southern and Southeast Asians
  - Cystic Fibrosis: Caucasians
  - Fragile X syndrome: All women (?)
- Family history of a genetic disease/chromosome disorder
- Maternal disease associated with increased risk of birth defects (diabetes, phenylketonuria)
- Known teratogen exposure during pregnancy
- Abnormal screening tests or ultrasounds
- Women who are concerned/worried
Prenatal Diagnosis Techniques

• Maternal Serum Screening Tests
  – Triple screen (alpha-fetoprotein, beta-HCG, and estriol) for neural tube defects and chromosome trisomies

• Visualization of the fetus
  – Ultrasound - 2D and 3D
  – Other (very special circumstances -X-ray, fetoscopy)

• Genetic and biochemical studies of fetal cells
  – Amniocentesis
  – Chorionic villus sampling
  – Fetal blood sample (percutaneous umbilical sample)
  – Circulating fetal cells in maternal blood
Maternal serum alpha-fetoprotein (MSAFP)

- Levels increase with gestational age in amniotic fluid and cross placenta into maternal bloodstream
- With neural tube (anencephaly, spina bifida) and body wall defects (gastroschisis, omphalocele) AFP is HIGH
- Using MSAFP along with detailed ultrasound study is sensitive to detect open body wall and neural tube defects
- MSAFP is LOWER in trisomies but using MSAFP alone to pick up trisomies is not sensitive or specific
- MSAFP most sensitive between 16-18 weeks
- To interpret must know gestational age, twin status, maternal health status (diabetes), and race - falsely high and falsely low values are often due to poor gestational dating
Maternal serum beta-human chorionic gonadotropin (MSb-hCG)

- Produced early by trophoblasts during pregnancy
- Elevated by first missed period and used as a pregnancy test
- Elevated hCG in the mid-late 2nd trimester in trisomies
- Most sensitive when used in correlation with MSAFP level
  - eg. MSAFP low AND MSβ–hCG high suggests increased risk of a trisomy
- VERY elevated hCG in the mid-late 2nd trimester along with an absence of a fetus suggests trophoblast disease (molar pregnancy)
Unconjugated Estriol (uE₃)

- Derived from adrenal gland hormone which is further metabolized by the placenta
- Synthesized from DHEAS, converted to 16αOH-DHEAS in fetal liver and then to uE3 by placenta
- Low levels associated with:
  - Trisomy 21
  - Trisomy 18
  - Triploidy
  - Smith Lemli Opitz
  - Steroid sulfatase deficiency
  - Fetal demise
  - Congenital adrenal hypoplasia
MSAFP vs “Triple Screen”

• Increased MSAFP alone is pretty sensitive for open body wall defects (eg. >95% for anencephaly, 80% for spina bifida)
• Decreased MSAFP alone is NOT very sensitive for trisomies (only 25%)
• “Triple screen” increases sensitivity (eg. to about 60% for Down syndrome)
• Use of more biomarkers further increases sensitivity, but no panel 100% sensitive or specific
<table>
<thead>
<tr>
<th>Disorder</th>
<th>AFP</th>
<th>hGC</th>
<th>hCG/AFP ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Spina Bifida</td>
<td>↑</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>Twins</td>
<td>↑</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>Fetal death</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
</tr>
</tbody>
</table>
Chorionic Villus Sampling

- Invasive technique to obtain fetal cells
- Study chromosomes, DNA, or biochemical profile of fetus
- Most often approached through the vagina but may be approached through the abdomen of the mother
- Most often performed between 10-13 weeks gestation, but as early as 9 weeks and any time after 13 weeks
- More genetic material from cells to study right away
- Risks:
  - Fetal loss rate slightly higher than amnio - about 1%
  - Very slight risk of increased limb abnormalities if done < 10 weeks
  - Risk of infection
Percutaneous Umbilical Blood sampling

- Invasive procedure to obtain fetal blood cells
- Study chromosomes, DNA, blood chemistries, or biochemical
- Needle under ultrasound guidance to obtain blood from umbilical vein
- Risks:
  - Fetal loss rate higher than amnio or CVS (at least 2% mid-2nd trimester)
- Rarely needed except in special circumstances where results can not be obtained by amniocentesis or CVS techniques
Amniocentesis

- To obtain amniotic fluid
- Needle is inserted into uterus through maternal abdomen
- Done after 14 weeks of pregnancy
- Done together with U/sound guide
- Perform only for strong clinical indication and if diagnosis cannot be made by un-invasive procedure
• Avoid
  – Specimen contaminated with maternal, or fetal blood and urine
  – Not fresh
Non-Invasive Prenatal Testing

• Detects cell-free fetal DNA in maternal serum
• Uses mass-parallel sequencing to amplify fetal DNA in order to perform genetic testing
• Currently reporting out increases in fetal DNA for chromosomes 13, 18 and 21
  – It is possible that lab will notify us if other numerical chromosome differences are detected
• In the future, it is possible that applications and reporting will expand
# verifi® NIPT Facts

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>~99.9%</td>
<td>100%</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>97.8%</td>
<td>100%</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>78.6%</td>
<td>100%</td>
</tr>
</tbody>
</table>

sensitivity = ability to correctly identify positive case

specificity = ability to correctly identify negative case
Detection of foetal abnormalities

• Diagnosed with use of maternal plasma or amniotic fluid.
• Amniotic fluid is obtain thru Amniocentesis at 14wks gestation
Neural tube defects

• Alpha-fetoprotein is abnormally high in severe form.
• Other causes of raised AFP
• Multiple pregnancy
• serious foetal abnormalities
• exomphalos
• AFP assay is done 16 to 18 wks of gestation
• High resolution uss is replacing it now
• Amniotic fluid acetylcholinesterase assay is now rarely used
Down’s syndrome:

- Low maternal AFP and unconjugated oestriol
- Raised hCG and inhibin-A.
- Ultrasound also have role to play
- A definitive test is amniocentesis with collection of fetal cells for karyotyping.
Others

- Chromosomal abnormalities and some inborn errors of metabolism:
  - detected by ;
  - cytogenetic
  - biochemical or enzymatic assays on cell cultured from amniotic fluid or biopsy of chorionic villi.
- In erythroblastosis foetalis ; Amniotic fluid Bilirubin is elevated.
- In pulmonary immaturity plasma lecithin/sphingomyelin ratio is low ie less < 2.
The goal of prenatal diagnosis is not to generate perfect babies. “The are no perfect human specimens - we are all genetically flawed in some way.”

- F.Collins