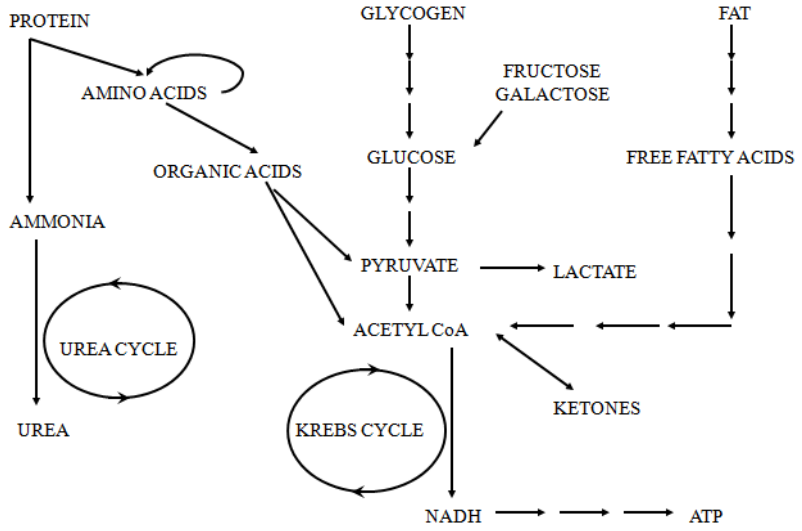
- **Metabolic disease are a combination of accumulation of metabolites which are usually toxic with energy insufficiency.**
  - There is an inherited enzyme deficiency leading to disruption of normal body metabolism with accumulation of toxic substrates and impaired formation of the product normally produced by the deficient enzyme.
- **You strongly suspect the presence of an inborn error of metabolism when there is a family history:**
  - Most inborn errors of metabolism are recessively inherited. Notice that a negative family history doesn't mean that the disease will not be present!
  - Consanguinity is a strong factor (usually resulting in expression of autosomal recessive disorders).
  - History of neonatal deaths or fetal losses may suggestive for the presence of these disorders.
  - Maternal family history:
    - ✓ Males only: X-linked disorders.
    - ✓ All affected: Mitochondrial DNA is maternally inherited.
- **The following diagram represents an integrated view of metabolic pathways:**



- **Laboratory assessments:**

Routine studies	Special studies
Blood lactate and pyruvate	Plasma amino acids
CBC and differential count	Plasma carnitine
Plasma ammonia	Urine amino acids
Plasma glucose	Urine organic acids
Plasma electrolytes and blood pH	
Urine ketones	
Urine reducing substances	

- **Indicators for neonatal screening tests:**
  - The condition is very important (e.g. can result in death!) and relatively common (not rare in the society).
  - There is an effective treatment for the condition.
  - The screening test is reliable and inexpensive with high sensitivity and specificity.
- **Indications for prenatal diagnosis:**
  - Diseases is serious and justify the termination of pregnancy. Notice that prents must be informed and accept to terminate pregnancy is fetus is affected with the condition.
  - There is no effective treatment for the disease.
  - There is a reliable and safe diagnostic test for early pregnancy.

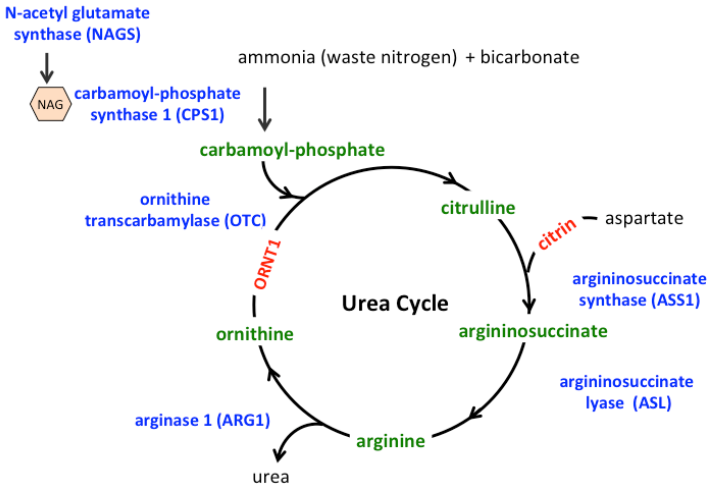
- **When there are acute neonatal symptoms, these are the initial investigations which you must do:**

Blood	Urine
CBC and clotting factors	Odor
Urea and electrolytes (for anion gap)	Ketones: ketonuria is an indicator for a metabolic disease in the newborn
Glucose	Reducing substances
Gases	pH
Uric acid	
LFT (Liver Function Test)	
Ammonia	
Lactate	
Calcium	

- **Further investigations include the following:**

Blood	Urine	Specific test	CSF (±)
Amino acids	Amino acids	Gal-1-PUT	Lactate
Carnitine (total & free)	Organic acids	-	Glycine
Acyl carnitines			

- **Urea cycle disorders:**



- **Ornithine transcarbamylase deficiency (X-linked).**
- **Carbamoyl phosphate synthase deficiency (autosomal recessive).**
- **Citrullinemia (autosomal recessive).**
- **Argininosuccinic academia (autosomal recessive).**
- **Argininemia (autosomal recessive).**

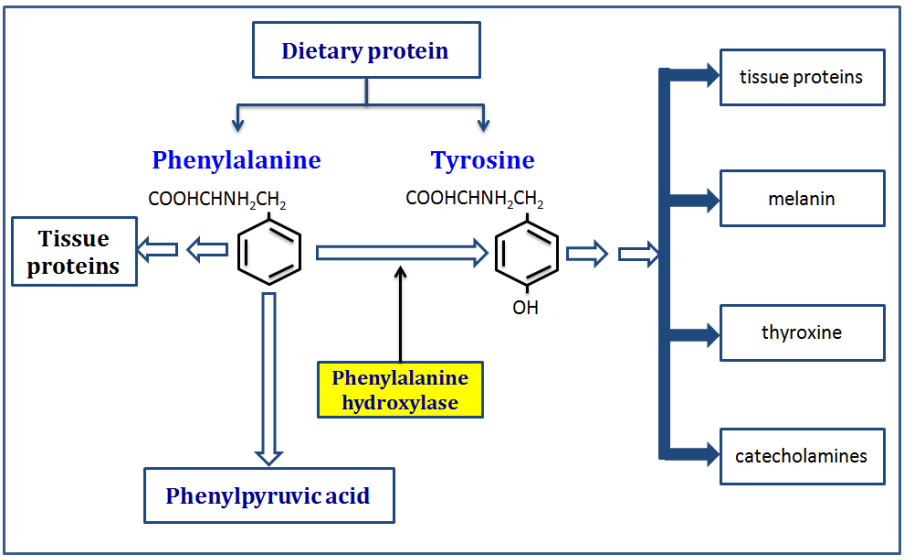
- **Organic acidemia:**
  - Organic acids are intermediates in the catabolic pathways to break down amino acids, lipids and other compounds to acetyl CoA and succinyl CoA which are entry points into the Kreb's cycle.
  - Urine organic acid analysis will show elevation of organic acids proximal to the enzymatic block; the resulting pattern is interpreted by the metabolic laboratory.

Disorder	Enzyme
• Methyl malonic Acidemia.	• Methyl malonyl COA mutase.
• Propionic Acidemia.	• Propionyl COA Carboxylase.
• Multiple carboxylase deficiency.	• Malfunction of all carboxylase.
• Ketothiolase deficiency.	• 2 methylacetyl COA thiolase def.

- **Urea cycle defects vs. organic acidemia:**

	Urea cycle defect	Organic acidemia
Lethargy/ coma	+	+
Vomiting	+	+
Hyperammonemia	+++	±
Metabolic acidosis	-	+
Respiratory alkalosis	+	-
Urine ketones	-	+

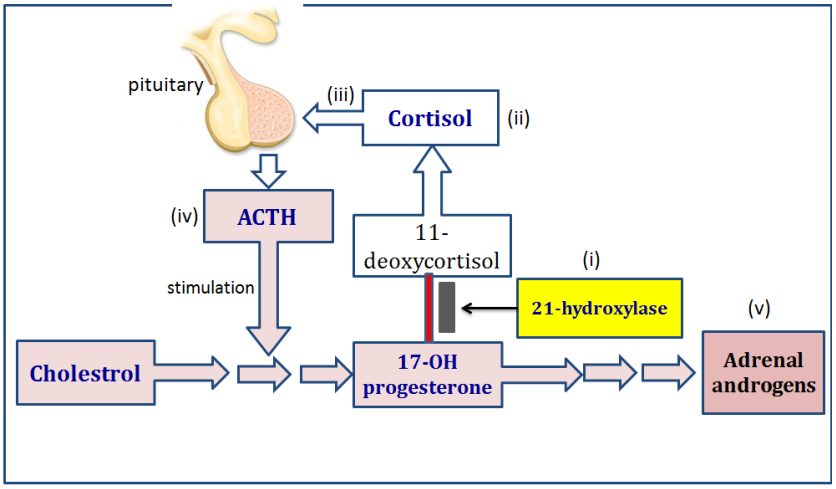
- **Phenylkeotnuria:**



- Deficiency of the enzyme (phenylalanine hydroxylase) which converts phenylalanine to tyrosine.
- Nowadays, it is not typically seen due to newborn screening.
- **Clinical manifestations**: newborn will be asymptomatic foe few months, then the following will appear:
  - ✓ Severe vomiting with irritability.
  - ✓ Eczema.
  - ✓ Mousy odor of urine.

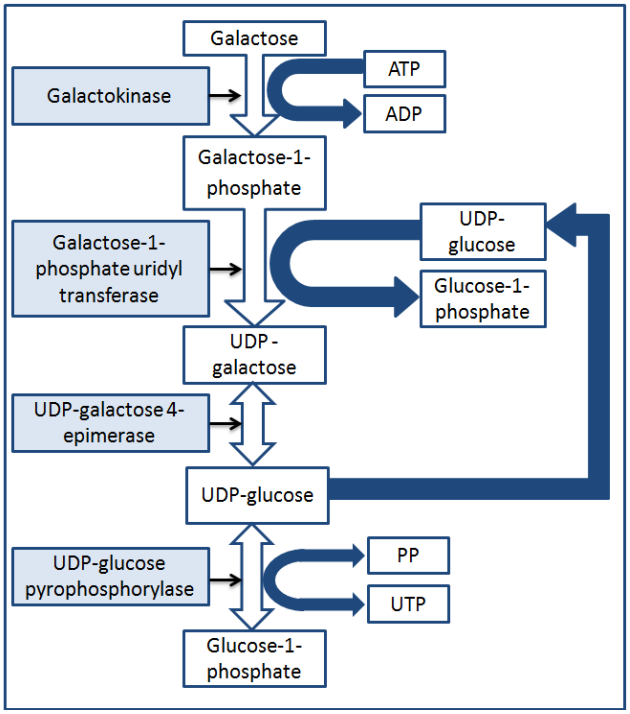
  Note: this deficiency is typically seen in those with blond hair and blue eyes☺
- **Treatment**: low phenylalanine diet (for life ☹!) + adequate tyrosine intake.

- **Steroid 21-hydroxylase deficiency:**



- It is an inherited autosomal recessive disease which results in decreased cortisol synthesis. This results in increased ACTH secretion from the pituitary which will increase synthesis is androgens from cholesterol.

- **Galactosemia:**



- There is deficiency of galactose-1-phosphate uridyl transferase.
- **Diagnosis**: enzyme assays on RBCs.
- **Clinical manifestations:**
  - ✓ Poor feeding with failure to thrive.
  - ✓ Vomiting and lethargy.
  - ✓ Jaundice with hepatomegaly.
  - ✓ Abdominal distention.
- **Investigations:**
  - ✓ Hypoglycemia.
  - ✓ Non-glucose sugars in the urine.
- **Treatment**: galactose-free diet (ophthalmology and developmental follow-up).

- **Techniques of prenatal diagnosis:**

Ultrasound	Visualizing internal body structures
Amniocentesis	Usually done when a woman is 14-16 weeks pregnant
Fetoscopy	Endoscopic procedure during pregnancy allowing assessment of the fetus
Chorionic villus sampling	Determining genetic or chromosomal disorders in the fetus
Percutaneous Umbilical cord Blood Sampling (PUBS)	Umbilical vein sampling