

# Prenatal screening of inborn errors of development

Prenatal genetic screening is a specific group of examinations which have one main goal: **to identify the pregnancies that are more risky** (considering the risk of genetic syndromes and disorders). The screening examination in general (and it applies also for the prenatal screening) has to meet some criteria, for example:

- The screening test has to be quite **easy to perform** (that ensures it is available for whole population).
- The screening test has to have **low cost** (which ensures the healthcare system can afford it).
- The screening test has to target diagnoses that are (relatively) **common** (it has no sense to screen population for extremely rare syndromes).
- The screening tests has to target **treatable** diagnoses (this is not exactly met by prenatal screening since you can not prevent the syndrome itself but it is possible to offer the termination of pregnancy).

The ideal screening examinations shall also have:

- Zero false positivity (screening positive, diagnosis not present).
- Zero false negativity (screening negative, diagnosis present).

The prenatal screening targeting genetic syndromes and disorders is nowadays **mainly focusing on chromosomal aneuploidies** (that is for example Trisomy 21 = Down syndrome as the most common/known example). These aneuploidies represent quite common findings, the screening positivity is quite easy to confirm/exclude (karyotype examination of the fetus).

The eldest screening method for chromosomal aberrations was the so called "advanced maternal age indication" where the mothers aged 35 years or more (at the planned date of delivery) were offered invasive prenatal diagnostics and karyotyping of the fetus. Nowadays, the pregnant women usually benefit from more sophisticated screening methods (see below), anyway the maternal age is always used as one of the variables for screening risk calculation and the sole advanced maternal age indication is still one of the reasons when the invasive prenatal diagnostic can be offered.

The screening tactics may differ among different countries and sometimes even also among different prenatal cares centres in the same country. In general we can see:

## Biochemical screening

### First trimester (combined) screening:

This screening method combines the maternal blood sampling (round 10th GW) and ultrasound examination of the fetus (round 13th GW).

The **biochemical part** uses (mostly) two biochemical markers: free beta subunit of human chorionic gonadotropine (**free-beta-hCG**) and Pregnancy-associated plasmatc protein A (**PAPP-A**). Low levels of PAPP-A and high levels of fb-hCG increases the theoretical risk of Down syndrome.

The **ultrasound part** is using several biometric values of the fetus, where the **nuchal translucency** (NT) size is the most important one (the normal results should not exceed the value of 2.0-2.5mm). The risk calculation can also include results of several utrasound markers, like nasal bone presence, tricuspidal valve leaking or ductus venosus flows.

The final result is usually calculated for trisomies 13, 18 and 21 and the calculation includes a) maternal age; b) ultrasound markers; c) biochemical markers.

### Second trimester (biochemical) screening:

Second trimester biochemical screening is the "classical" screening method, older then first trimester screening. The classical form of this screening uses three biochemical markers (used to be called as a "triple test"): alpha-fetoprotein (AFP), unconjugated estriol (uE3) and human chorionic gonadotropin (hCG).

- High levels of hCG along with low levels of AFP and uE3 signalize higher risk of Down syndrome.
- High levels of AFP are showing possible risk of neural tube defects (or generally structure defects uncovered by fetal skin).
- Low levels of hCG/AFP/uE3 together signalize possible risk of Edwards syndrome or triploidy.
- Very low levels of uE3 may signalize metabolic defect of cholesterol synthesis (Smith-Lemli-Opitz syndrome).

## Integrated screening

Some laboratories are evaluating the results of 1st and 2nd trimester screening together as so called **integrated screening**.

## Ultrasound screening

Ultrasound examination in pregnancy is quite common and most pregnant women have numerous ultrasound examinations performed during the pregnancy. The number and timing of ultrasound examinations is very different in different countries and also differs among different prenatal diagnostic centres even in the same country. We can mostly encounter:

- First ultrasound in 4-8th week of pregnancy: usually performed in order to confirm the pregnancy and to identify twin pregnancies.
- Combined screening ultrasound: usually performed as a part of first trimester combined screening (around 13th week of gestation). Main goals are the basic parameters measurements (BPD, HC, NT etc.) and also the general visualization of the main organ structures (brain, hearth, limbs).
- Detailed ultrasound examination: usually performed between 18th and 22th week. This examination is mainly focused on the identification of any structural anomalies that can be observed in the fetus.
- Third trimester visualization: performed in the third trimester in order to evaluate the size of the fetus and any possibly pathological findings that can influence the approaching delivery.