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## Alpha-Fetoprotein as a Biomarker Not Classified Only for Pregnancy, but also Different Levels Might Show Problems in Another Organ Systems [Part 1]

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## 1. Summary

Alpha-fetoprotein [AFP] is a protein normal made by the yolk sac, intestines and liver of a developing foetus. AFP levels go down soon after birth, so healthy children and adults usually have very little AFP in their blood. A higher level of AFP in the blood may also mean that there is something wrong in the liver. In this article we will point out problems clinicians may face while getting results of AFP levels out of physiological range in pregnancy (Figure 1) and levels out of range in different organ systems.

Weeks of Pregnancy	AFP (IU/mL)
10	Sep-24
11	Oct-27
12	Oct-30
13	Oct-34
14	Nov-60
15	14-60
16	16-69
17	17-78
18	22-93
19	32-103
20	42-121
21	48-139
22-24	56-224
25-27	95-357
28-30	135-435
31-33	141-423
34-36	121-380
37-40	93-321

Figure 1: Levels of AFP according to gestational age

## 2. Introduction

Alpha-fetoprotein is among the most widely used diagnostic biomarkers based on its use for screening for malignancies and prenatal abnormalities. AFP still remains an important biomarker for physicians and another study are needed to determine whether AFP has a functional role in these processes.

Why an AFP test is done

The AFP test can be ordered for different reasons. For the following cancers it can help with diagnosis measuring your response to treatment and checking if the cancer has come back /recurred/:

- Ovarian germ cell cancer
- Non-germinal testicular cancer
- Extragonadal germ cell cancer [a type of cancer that develops from germ cells outside of the gonads]
- Liver cancers

In some cases, an AFP test can be used to help diagnose the following cancers:

- Bile duct
- Stomach
- Colon
- Pancreas
- Lung

- Lymphoma
- Childhood central nervous system [CNS] germ cell cancer [for example, non-germinatous cerm cell tumors]
- Cancer of unknown primary [CUP]

There is also possibility to have AFP test to help manage liver problems such as cirrhosis or infection with hepatitis virus B or C. During pregnancy, an AFP test may be done to screen for birth defects of genetic disorders. AFP is measured in a sample of blood taken through a needle. An AFP test is usually done in private of hospital lab. No special preparation is needed, except in children where we need to control their anxiety and make them more cooperative and develop their coping skills. If a change or abnormality in results occurs, there should be done more tests, procedures, follow-up care or additional treatment [1].

First of all the clinicians should look at the previous results of patients' AFP test, along with other test results, to help diagnose and treat them.

Higher than normal AFP levels in the blood may be a sign of a germ cell tumour or liver cancer. These types of cancer can release AFP into the blood, but also in non-cancerous conditions such as:

- Cirrhosis
- Hepatitis
- A rare inherited disorder called ataxia-telangiectasia

AFP synthesis is reactivated in liver tumours and germinogeneous teratoblastomas, in a lesser degree after chemical or mechanical liver injuries followed by regeneration [for example acute viral hepatitis] [2]. But also, should be considered that for some people, a slightly higher AFP levels may be normal.

### 3. Alpha-Fetoprotein Connected to Pregnancy and Genetics

Alpha-fetoprotein is a well-known diagnostic biomarker used in medicine to detect fetal developmental anomalies such as neural tube defects or Down's syndrome, or to follow up the development of tumors such as hepatocellular carcinomas. The AFP gene is a member of a multigenic family that comprises the related genes encoding albumin, alpha-albumin, and vitamin D binding protein. The biological role of this major embryonic serum protein is unknown although numerous speculations have been made. AFP is a glycoprotein that is normally produced by the fetal yolk sac, liver, and gastrointestinal tract. Abnormal AFP levels can be found in newborns but not in adults. Elevated serum levels of AFP, a fetal serum protein, occur mainly in the development of hepatocellular carcinoma [HCC] or germ cell tumours, mainly yolk sac tumor. Rarely other tumors of the urogenital system produce AFP. Human AFP is a tumor-associated fetal mammalian glycoprotein involved with both otogenic and oncogenic growth. AFP is an oncofetal protein found in increased levels in hepatocellular carcinom, liver

metastasis and other benign liver diseases. AFP is a marker related to embryonic development [yolk sack]. mainly used for diagnosing germ cell tumors and liver tumors. Elevated AFP concentrations may be observed in cirrhotic patients during a flare-up chronic hepatitis, or during the recovery phase postacute hepatitis.

#### 3.1. Genetics

AFP tests are good tools for detecting genetic disorders or neural tube defects. Up to 9 in 10 fetuses with neural tube defects were diagnosed because the AFP test detected anomalies. But AFP tests aren't perfect. In every 1,000 pregnant people who get the AFP test, up to 50 get abnormal results.

#### 3.2. Is high AFP genetic?

Very rarely, incidental detection of raised AFP in a genetically susceptible individuals has been reported in the absence of the underlying malignant process. This condition is termed as hereditary persistence of AFP [hpAFP], a rare disorder with an autosomal dominant pattern of inheritance [3].

#### 3.3. Can AFP be false-positive?

If a particular concentration of AFP, the „cut-point“, is chosen as an indication of the presence of an abnormal fetus there will be false-positives and false-negatives, because some normal pregnancies are associated with higher AFP concentrations than are some affected pregnancies.

#### 3.4. Can infection cause high AFP?

Thus, falsely elevated AFP levels [100 ng/mL] were caused most fused by HBV and HCV infection. In patients with CHB, elevated AFP levels were not persistent and were consistent with serum ALT levels and the presence of the bridge fibrous in 80% of patients with AFT levels 100 ng/mL.

#### 3.5. Can hepatitis increase AFP?

Serum AFP is also elevated in some non-hepatic malignancies and in conditions such as acute or chronic hepatitis. 9,10 Serum AFP may also be elevated in patients with CLD due to hepatitis B or C. The frequency of elevated serum of AFP may also be elevated in patients with CLD due to hepatitis B and C infection.

### 4. Alpha-Fetoprotein [AFP] Test in Pregnancy

It is a test that is mainly used to measure the level of AFP in the blood of a pregnant woman. The test checks the baby's risk for having certain genetic problems and birth defects. Some AFP passes from the baby into the pregnant woman's blood. Certain conditions can make a baby's body release more or less AFP. During pregnancy, if your blood levels are higher or lower than normal, it may be sign that:

The baby has a high risk of having a genetic disorder, such as:

- A neural tube defect, which is a serious condition that causes abnormal development of a developing baby's brain and/or spine.

- Down syndrome, a genetic disorder that causes intellectual disabilities and other health problems
- Might be that the estimated due date is wrong, so an abnormal AFP may mean that your baby is due earlier or later than estimated. This is the most common reason for abnormal AFP levels
- Pregnancy with more than one baby – each baby makes AFP, so the AFP blood levels will be higher with two or more babies.

So, in case your AFP test results aren't normal, it means you need more testing to find out whether your baby has a health problem. If you are pregnant, AFP test is routinely offered between the 15th and 20th week of pregnancy. Your provider may especially recommend the test if you

- Have a family history of birth defects
- Are 35 years or older
- Have diabetes
- Have used medicines or drugs during pregnancy

The most common cause for abnormal AFP test results during pregnancy is an error estimating your due date. But a result that isn't normal may also be in a sign of possible problems:

- Lower than normal AFP levels may mean your baby has a genetic disorder such as Down syndrome, a genetic disorder that causes intellectual disabilities and health problems.
- Higher than normal AFP levels may mean your baby has an increased risk of having a neural tube defect, such as:
  - Spina bifida, a condition in which the bones of the spine don't close around part of the spinal cord
  - Anencephaly, a condition in which the brain do not develop properly
  - high AFP levels may also mean that you are having more than one baby. You may. Also get a false-positive result. That means that your AFP results aren't normal, but your baby is healthy.

If your AFP test results aren't normal, you will likely have more tests to help make a diagnosis.

AFP tests are often part of a group of prenatal tests called multiple marker or triple screen test. These tests can help diagnose Down Syndrome, trisomy 18 [Edwards syndrome], and other genetic disorders. A triple screen test includes test for:

- Alpha-fetoprotein [AFP]
- Human chorionic gonadotropin [HCG], a hormone produced by the placenta
- Estriol, a form of estrogen made by the baby and the placenta

In some cases, a fourth test is included, called an inhibin A test,

which helps diagnose Down syndrome.

Your provider may also recommend a test called prenatal cell-free DNA [cfDNA] screening. This is blood test that can be done as early as the 10th week of pregnancy. It can show if your baby has a higher chance of having Down syndrome or certain other genetic disorders.

Related medical tests:

- Amniocentesis [amniotic fluid test]
- Chorionic Villus Sampling [CVS]
- Down Syndrome Tests
- Estrogen Levels Tests
- Karyotype Genetic Test
- Ultrasound [3]

For people who aren't pregnant, an AFP test may be used to help diagnose certain cancers that may cause high AFP levels in adults. When the test is used this way, it's called an AFP tumor marker test.

## 5. Can a Pregnancy Test Predict Testicular Cancer?

Pregnancy tests work by detecting human chorionic gonadotropin [HCG], a hormone in the blood and urine produced by the developing placenta.

It turns out that some types of testicular cancer make the same hormone.

Some forms of testicular cancer cause elevated HCG levels, but others don't. Someone could get false reassurance from a negative test of could have elevated HCG levels for another reason altogether.

Men should go see a doctor if they notice testicular cancer symptoms or unusual changes, including a lump or enlargement in either testicle a sensation of heaviness in the scrotum, or a sharp pain or discomfort in the scrotum or testicle. It is recommended to perform a self-exam in the shower once a month, starting in puberty.

### 5.1. Testicular Cancer Risk Factors

Compared to other types of cancer, testicular cancer is rare, accounting for just 1% of all cancers that occur in men. Yet it's the most common cancer in males ages 15 to 35.

The disease occurs when cells in the testicles grow and multiply out of control causing tissue damage and disrupting the normal function of the testicle.

The exact causes of testicular cancer are unknown, but a number of factors have been identified that increase a man's risk of developing the disease, including undescended testicles at birth, a family history of testicular cancer, or a previous testicular cancer diagnosis.

### 5.2. How is Testicular Cancer Diagnosed?

A scrotal ultrasound – it is usually the first step in diagnosing testicular cancer. It is painless procedure and gives clear indication

of whether a mass in the testicle is solid or filled with fluid. A fluid-filled lump is usually harmless. A more solid lump may signal that the swelling is cancerous. The next step is a blood test. Many testicular cancers make high levels of certain proteins called tumor markers such as HCG and alpha-fetoprotein [AFP], which are both associated with pregnancy. When these tumor markers are in the blood, it suggests that there's a testicular tumor.

### 5.3. How is Testicular Cancer Treated?

The first treatment for all cases of testicular cancer, whatever the stage, is an orchiectomy – a surgical procedure to remove the testicle. By removing the entire affected testicle, your chances of making a full recovery are greatly improved. Removing only the tumor may result in the cancer spreading. Sex life and the ability to father children are typically not affected. After surgery, doctors monitor HCG level to determine if the cancer is gone.

### 5.4. Testicular Cancer Survival Rates

Testicular cancer is highly treatable, even when cancer has spread beyond the testicle. While a cancer diagnosis is always serious the good news about testicular cancer is that the vast majority of cases – even if they are caught further along – are still very curable [4].

## 6. Role of AFP in Diagnosing Childhood Cancers and Genetic-Related Chronic Diseases

AFP is a protein commonly found during fetal development, but its role extends beyond birth. Throughout the first year of life, AFP levels can remain high, which can potentially mask various conditions from the neurological, metabolic, hematological, endocrine, and early childhood cancer groups.

Sources of elevated AFP in infancy and childhood

- Intracranial germ cell tumors [IC-GCTs] – account for 0,3-3,4% of childhood CNS tumors in North America and Europe. These tumors can be categorized into two main types: germinomas [GER] and non-germinoma GCTs [NG-GCT]. Intracranial teratomas are the most common, followed by immature teratomas.
- Germ Cell Tumors - account for 3,5% of cancers in children up to the age of 15 and 13,9% in the 15-19 age group. They are characterized by male dominance. These tumors are commonly found in midline locations of the body, such as the sacrococcygeal region, mediastinum, skull, retroperitoneal space, nasopharynx, orbit, neck, uterus, and vagina.
- Hepatoblastoma [HB] – is the most common malignant liver tumor in children, accounting for 67-80% of cases.
- Hepatocellular carcinoma [HCC] – is the second most common malignant liver tumor in children, accounting for 2-33% of cases. Surgical treatment, including complete tumor resection [possible in only 30% of diagnosed cases] along with additional chemotherapy or liver transplantation, is the standard approach for managing HCC.
- Ataxia teleangiectasia [AT] – The condition occurs with a

frequency of 1:40,000 to 1:100,000 live births. In 90% of patients, AFP levels are elevated. There are several hypotheses regarding elevated AFP levels in certain conditions. The first hypothesis suggests that the increase in AFP is associated with progressive liver damage. The second hypothesis focuses on the role of the suppressor protein TP53, which plays a role in DNA damage repair and also acts as a repressor of the gene responsible for AFP synthesis during liver development and regeneration. A third hypothesis suggests that AFP synthesis increases in response to the damaged CNS' need for building blocks for cell membranes during the process of myelination.

- Primrose syndrome – The clinical presentation of the condition includes intellectual disability macrocephaly, high post-natal growth, cataracts, deafness, auricular calcifications, and myopathy.
- Tyrosinemia type I – The condition is found in approximately 1:100,000 births. This mutation results in a deficiency of fumarylacetoacetase hydrolase, leading to the accumulation of toxic tyrosine metabolites, namely fumarylacetoacetate and maleylacetoacetate, in the liver and kidneys. These metabolites have mutagenic properties and inhibit porphobilinogen synthesis, leading to porphyria-like seizures.
- Progressive familial intrahepatic cholestasis [PFIC2] – This mutation disrupts the normal transport of bile from hepatocytes to the bile ducts, resulting in its accumulation within hepatocytes. This leads to chronic inflammation and carcinogenesis. The disease progresses rapidly, resulting in cirrhosis HCC, biliary tract cancer, and liver transplantation.
- Transaldolase deficiency [TALDO] – Transaldolase is an enzyme produced in the liver that plays a role in the pentose phosphate pathway. Deficiency of this enzyme results in a defect in the pentose phosphate pathway and the accumulation of polyols in the blood, urine, and CSF. Elevated AFP levels serve as a marker of liver regeneration and tumorigenesis.
- Hepatitis B [HBV] – The infection is primarily transmitted vertically in newborns while in contrast to adults, where only 5-10% develop chronic hepatitis when infected, 25 – 90% of infected newborns experience chronic hepatitis. Furthermore, persistently high AFP levels for over a year despite antiviral treatment significantly contribute to the development of HCC. HBV-related HCC in children predominantly affects males, occurs later in life, and tends to be more aggressive compared to HCC caused by other factors.
- Malignant sacrococcygeal GCT – the occurrence of SCT has a frequency of 1 in every 35,000 – 40,000 births. This condition is more prevalent among girls. Typically, before the age of 3, with an inward-growing growth pattern characterized by buttock asymmetry and gastrointestinal and/or urinary tract issues, as well as lower limb dysfunction.

- Fanconi anemia congenital hypothyroidism – is inherited in an autosomal recessive manner. The genetic basis of the condition involved numerous mutations, approximately 19 in total, that affect genes responsible for DNA repair [5].

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