Review Article

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Role of Alpha Fetoprotein in Obstetrics

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Abstract

Screening in pregnancy is of surveying a population of women with markers to identify those at higher risk of particular disorder. Biochemical markers are building blocks for screening tests. Alpha-fetoprotein is used to identify pregnancies at high risk of neural tube defects. Its implication extended beyond NTDs screening to detection of other anatomic malformations, multiple pregnancy, Down's syndrome, other aneuploidies and placental disease. There are variables affecting serum AFP. Estimation of maternal serum alpha- fetoprotein is found to be one of the cost effective and non-invasive screening method.

Keywords: Alpha Fetoprotein; Screening Tests; Biochemical Markers; Neural Tube Defects.

Introduction

While pregnancies and childbirth are natural events, they often require medical interaction and intervention. Every pregnancy has some degree of potential risk. George Orwell srates:

"In clinical practice some pregnancies are more at risk than others."

The goal of every obstetrician should be to give the best prenatal care to the fetus to achieve an optimal perinatal outcome. The success of antenatal care is reflected in the reduced maternal mortality, morbidity and fetal salvage.[1] We are on the threshold of a new and far more important type of antenatal care, and since prevention is always better than cure, it is the aim of antenatal care to reduce the need for desperate measures at the time of delivery.[2] Following success of maternal care, obstetricians turned their attention towards improvement in the health. Screening in pregnancy is of surveying a population of women with markers to identify those at higher risk for a particular disorder. Such women can then be offered further diagnostic tests and appropriate treatment to reduce their risk and/or any complication arising from the disease or condition. Nowadays physicians are able to perform detailed diagnostics of unborn fetuses, a possibility being not more than pure science fiction only 50 years back in time. Prenatal diagnosis can be done invasively, non invasively and went through many steps of development.[3]

Biochemical markers are the building blocks of screening tests. The earliest example of prenatal screening is the use of a single second trimester maternal serum marker, alpha-fetoprotein, to identify pregnancies at high risk of neural tube defects. Its implication extend beyond NTDs screening to detection of other anatomic malformations (Gastroschisis, Omphalocele Etc.), multiple pregnancy, Down's syndrome and other aneuploidies and placental disease.[4]

Alpha-fetoprotein (AFP), whose existence was identified in 1956 in two separate laboratories during electrophoretic experiments is the homologue of a serum protein found in all mammalian species during embryonic development.[5] Alpha Fetoprotein is a fetal glycoprotein that is initially produced in fetal yolk sac

and liver and in small amount by fetal gastrointestinal track. By the end of the first trimester nearly all hormones are produced by fetal liver. Its peak can occure between 10-13 weeks. This fetal AFP diffuses across placental barrier into the maternal circulation. A small amount is transported from amniotic cavity.[6]

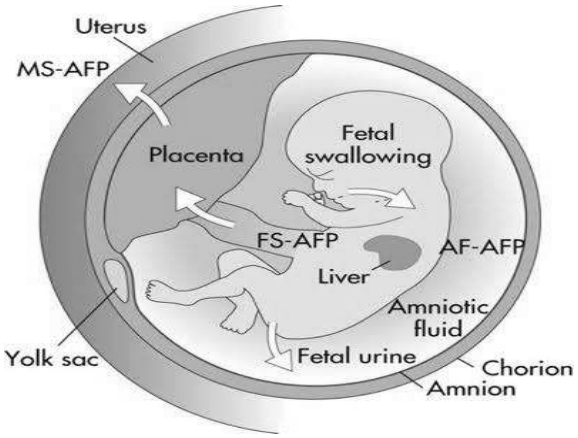

Fig no. 1: Robbin M, Filly RA, Fell S, Goldstein RB, Callen PW, Goldberg JD, Golbus MS. Elevated levels of amniotic fluid alpha-fetoprotein: sonographic evaluation. Radiology. 1993 Jul;188(1):165-9.

Table no. 1: Alpha Feto Protein.

Alpha Feto Protein (AFP)
Size-70,000 Daltons
Half-Life - 5-7 days
Normal Range - <40µg/l

Ref. 7: Mizejewski GJ (2001) Alpha-fetoprotein structure and function: relevance to isoforms, epitopes, and conformational variants. Exp Biol Med (Maywood) 226:377-408.

Table no. 2: Concentration of AFP in Serum.

First 2 Months of Life	400 ng/ml
6 Months	30 ng/ml
1-2 Years of Age	<15 ng/ml
Childhood and Adult Life	3-15ng/ml

Ref. 8: Stanley Yachni N, The clinical significance of human alpha fetoprotein, Ann clin lab sci Mar-April 1978.

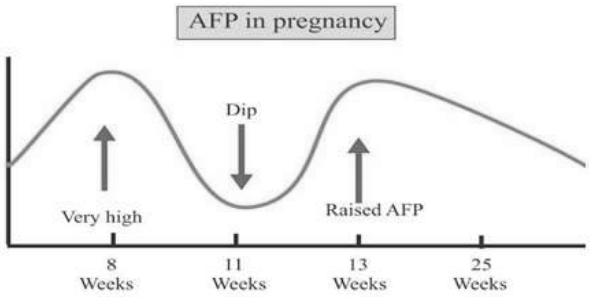

Fig. no. 2: Tucker JM, Brumfield CG, Davis RO, Winkler CL, Boots LR, Krassikoff NE, Hauth JC. Prenatal differentiation of ventral abdominal wall defects. Are amniotic fluid markers useful adjuncts? J Reprod Med. 1992 May;37(5):445.

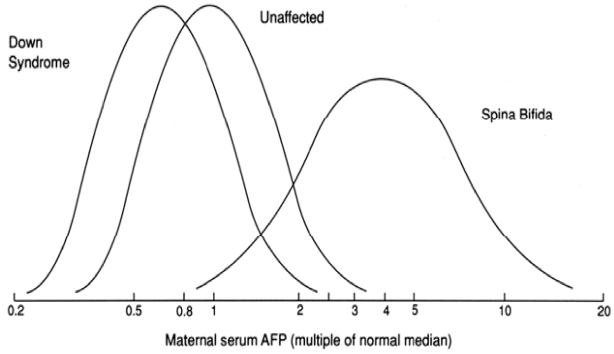

Fig no. 3: Crandall BF, Chua C. Risks for fetal abnormalities after very and moderately elevated AF-AFPs. Prenat Diagn. 1997 Sep;17(9):837-41.

In developing countries because of transport problems, financial restraints or inability to spare the time to visit the clinic, first trimester screening is still not routine and thus second trimester biochemical screening has an important role in such women. One of the important second trimester markers for biochemical screening is MSAFP. Maternal Serum Alpha-Fetoprotein is a protein not synthesized by normal adult tissues. It is produced by fetus. It enters both into the amniotic fluid and maternal circulation, in amounts commensurate with the gestational age. Its estimation between 14 -18 weeks of gestation correlates with the possibility of congenital malformation. MSAFP is one of the most important screening tools.[9]

In fetus with neural tube defect this hormone leaks directly from defect into the amniotic fluid causing high concentration of AFP. Subsequently this AFP reaches the maternal circulation. Thereby resulting elevated MSAFP. The test is conducted at 16-18 weeks of gestation. The serum AFP levels of patient are measured and compared to median AFP value in an unaffected population to obtain a multiple of median (MOM). The MOM cutoff of 2.5 MOM, classifies the test is screen positive or screen negative.

Measured maternal serum AFP concentration are provided by maternal characteristics and variables from medical history. Serum AFP increases with increasing gestational age and decrease with greater maternal weight.

Variables Affecting Serum AFP:

- Gestational Age at Assessment
- Maternal Weight
- Parity Status
- Racial Origin
- Cigarrete Smoking
- Gestational Age at Delivery
- Z-Score of Neonate in Previous Pregnancy
- Interpregnancy Interval[10]

Discussion

AFP is synthesized in early S1 phase of the cell cycle and is secreted prior to the M phase. The production of HAFP is initiated at the level of gene transcription and is

proportional to the amount of available mRNA. Secretion of AFP from the hepatic oval cells occurs soon after synthesis with only minimal storage in the liver.[11]

Measurement of MSAFP is performed to detect fetal neural tube defects and fetal ventral wall defects. During pregnancy alpha fetoprotein is produced in sequence by the fetal yolk sac, the fetal gastrointestinal track and finally the fetal liver. Excretion of AFP in fetal urine results in high levels of AFP in amniotic fluid. Transfer of AFP to maternal serum occurs via the placenta and transamniotically. The interpretation of MSAFP screening test is the gestational age dependent and should be performed at the 15 to 20th weeks of pregnancy. Elevated maternal serum [>2.5 multiples of median] and amniotic fluid AFP [by Amniocentesis] can lead to suspicion of 85% of anomalies. According to the concentration of these biomarkers risk for fetal trisomies is assessed for each individual. Amniocentesis is offered in second trimester in cases who need confirmation.[12]

Table no. 3: MSAFP Is Component of following tests:

	MSAFP test	Triple test	Quadruple test
Components	MSAFP	MSAFP, hCG, Ue	MSAFP, hCG,uE
Time (weeks)	15-20	15-18	15-20
Observation	MSAFP[↑]	MSAFP[↓] hCG[↓] uE[↑]	MSAFP[↓] hCG[↓] uE[↑] Inhibin A[↑]
Detection Rate	85%	73%	85-92%
False positive rate	3-5%	5%	0.9%
Comment	Cut off level of 2.5 MOM can detect 90% of anencephaly, 80% open spina bifida	A cut of value of 1 in 200 is screen positive	Detection rate is high

Integrated Test: Performed in both First and Second Trimester PAPP-A (First trimester) +Triple/Quadruple test

Ref. 13: DC Dutta, Prenatal genetic counseling screening and diagnosis, Hiralal Konar, DC Duttas textbook of obstetrics 8th edition Jaypee Publication, New Delhi.

Table no. 5: Conditions Associated with Abnormal MSAFP Levels.

Elevated levels:

- Neutal tube defects (due to leakage into maternal serum)
- Abnormal vault defects (Gastroschisis, Omphalocoel, Bladderextrophy) (leakage into the maternal serum)
- Oesophageal Atresia
- Duodenal Atresia
- Renal Anomalies(Congenital nephrosis,Polycystic Kidney/Absent kidney,Urinary obstruction)
- Other Anomalies like Cystic Hygroma, Osteogenesisimperfecta, Sacrococcygeal teratoma
- Multiple pregnancy
- Intrauterine Death (leakage from broken skin)
- Placental Chorioangioma
- Maternal hepatoma and Teratoma
- Low maternal weight
- Preterm Delivery
- Low birth weight
- Underestimated gestation

Low levels

- Chromosomal Trizomies (Trizomy 21, Trizomy 18)
- Insulin dependent Diabetes mellitus
- Overestimated gestational age
- High maternal weight
- Gestational Trophoblastic disease

Ref. no. 14: Dr. J.B. Sharma, Genetics, Congenital Malformations, Prenataldiagnosis, Fetal Therapy, Teratology and Drugs during pregnancy and lactation, Dr. J.B. Sharma textbook of obstetrics, Avichal Publishing Company 2014.

Table no. 6. Aneuploidies Associated with AFP.

Aneuploidies	AFP
Down's Syndrome	Low
Turner's Syndrome	Decreased
Edward's Syndrome	Unchanged
Patau's Syndrome	Increased

Ref. no. 15: Gary Cunningham;Kenneth J,Prenatal Diagnosis,F.GaryCunningham;KennethJ;Steven L. Bloom;Catherine Y. Spong;WilliamsObstetrics;Mc Graw hill education,24th Edition.

Positive screen result indicates that further evaluation required. It can also be combined with other serum markers to obtain a triple marker test by inclusion of serum oestriol and beta hCG.[16] A strong association between second trimester elevated MSAFP level and adverse pregnancy outcome (preterm birth, preeclampsia, oligohydramnios, IUGR, placental-abruption, PPROM, IUFD, stillbirth, neonatal death) was found in a study conducted by Urmila Karya et al. Boyd et al proposed that 2nd trimester AFP elevation in a normally formed fetus is due to changes in the placenta which has the property of responding to an adverse environment by increasing its surface of exchange. Women with abnormal levels of AFP are offered a targeted ultrasound and amniocentesis if indicated. Even in absence of anomalies raised MSAFP may be associated with poor pregnancy outcome necessitating careful monitoring.

Brazerol et al reported elevated MSAFP as a marker of placental dysfunction:

- Partial placental abruption
- Fetomaternal bleeding
- Abnormal implantation

Alpha fetoprotein concentration can be determined framing others from invasively acquired amniotic fluid. AF-AFP-test continues to be widely applied in invasive prenatal diagnostics. Still, its predicative value is matter of debate.[15] There are many ethical considerations in the practice of fetomaternal medicine. Our objective is to avoid preventable death, disease or disability in children.

Counselling

Counselling is the vital part of any screening programme. It should include pre-test and post-test counselling. Pregnant women should be well informed about all implications prior to screening and options if the screen test is available. They must be aware of signs and symptoms of complications. They should be advised to undergo frequent antenatal check-up and testing by other modalities. The screening test should be acceptable to expectant mother.

Conclusion

Screening pregnant women in second trimester for maternal serum alpha-fetoprotein levels is recommended as it would help to identify high risk pregnancies, allow close antenatal surveillance for a better pregnancy outcome. Estimation of maternal serum alpha-fetoprotein is found to be one of the cost effective and non-invasive screening method. Measurement of serum AFP may be useful in screening for aneuploidies, neural tube defects and adverse pregnancy outcome. Effective use of serum AFP in risk assessment and screening necessitates that variables from maternal characteristics and medical history affecting measurement in normal pregnancy are taken into account.

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