Should "Transformed Alpha-fetoprotein" be considered a Potential Biomarker for Adverse Term Pregnancy Risk: An Opinion Letter

Gynecology and Women's Health Care

Opinion Letter

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Human alpha-fetoprotein (HAFP), classified as a tumor-associated fetal protein, has been reported in the biomedical literature to display multiple molecular forms and complexes. Such forms have been demonstrated to include the following: 1) circulating serum full length HAFP; 2) non-secreted cell-bound cytoplasmic HAFP forms; 3) truncated mRNA expressed/translated forms largely found in cell culture supernatants; and 4) serum circulating inter-molecular complexed forms [1, 2]. Moreover, the native 70 kD circulating serum AFP form has long been employed in the clinic as a "gold standard" biomarker for hepatocellular carcinomas and germ cell tumors in addition to being a biomarker for fetal birth defects.

More recently, a novel pregnancy biomarker termed "Transformed alpha-fetoprotein (TAFP)" appeared on the clinical scene during the 2007 to 2009 years (see below). TAFP is a molten globule slightly denatured form of AFP found in both man and animals. The existence of a TAFP form was known from multiple preclinical reports and observations of a conformationally altered form of AFP following exposure to high concentrations of estrogens, fatty acids, and growth factors [3]. The altered tertiary form of full-length HAFP unveiled a concealed or buried segment consisting of an intrinsic 34-amino acid sequence, later termed the "Growth Inhibitory peptide (GIP). This peptide fragment from AFP has been synthesized, purified, and characterized [4].

Rabbit antibodies to TAFP were produced and were not found to cross-react with full-length AFP as determined by commercial radioisotope, fluorescent, and ELISA assays. In contrast, rabbit antibodies to TAFP reacted only with HAFP when the TAFP (GIP) segment was exposed as observed in pregnancy maternal serum. This unveiling occurs following maternal serum HAFP exposure to fetal stress/shock environments at the uterine/placental interface. It is at this interface where high concentrations of estrogens and polyunsaturated fatty acids abound [5]. Fetal HAFP is known to be transferred from fetal serum to the amnionic sac compartment of the placenta where it diffuses into the maternal circulation via amniotic fluid [5, 6]. As discussed above, a maternal serum antibody assay for TAFP was developed and employed to quantitate TAFP levels in late third trimester pregnancies. Measurement of TAFP levels were used in the clinic to assess fetal well-being and adverse perinatal outcomes. The presence of TAFP levels in maternal serum were found useful in predicting risks of fetal distress and deterioration in pregnancy conditions such as: 1) fetal growth restriction / intrauterine growth retardation; 2) fetal chronic hypoxic stress; 3) threatened pre-term labor; and 4) fetal hemodynamic re-distribution [7-10]. These reports lend credence in support of the potential use of maternal serum TAFP as a candidate late pregnancy biomarker. Such a biomarker might be useful in assessing and/or predicting risks of adverse perinatal outcomes and heightened fetal distress in late third trimester pregnancies.

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References

1. Mizejewski GJ (2019). Protein binding and interactions with alpha-fetoprotein (AFP): A review of multiple AFP cell surface receptors, intracytoplasmic binding, and inter-molecular complexing proteins. *Journal of Molecular and Cellular Biology Forecast*, 2, 1016-1023.

2. Muehlemann M, Miller KD, Dauphinee M and Mizejewski GJ (2005). Review of growth inhibitory peptides as biotherapeutic agent for tumor growth, adhesion, and metastasis. *Cancer & Metastases Reviews*, 24, 441-467.

3. Vallette G, Vranckx R, Martin ME, Benassayog C and Nunez EA (1989). Conformational changes in rodent and human

alpha-fetoprotein: Influence of fatty acids. Biochimica et Biophysica Acta (BBA) - *Protein Structure and Molecular Enzymology, 997*(3), 302-312.

4. Mizejewski GJ and Butterstein G (2006). Survey of functional activities of alpha-fetoprotein derived growth inhibitory peptides: Review and Prospects. *Current Protein & Peptide Science, 7*(1), 73-100.

5. Bennassayag C, Rigoud V, Hassid J and Nunez EA (1999). Does high polyunsaturated free fatty acid level at the feta-maternal interface alter steroid hormone message during pregnancy? Prostaglandins, *Leukotrienes and Essential Fatty Acids, 60*(5-6), 393-399.

6. Haddow JE, Macri JN and Munson J (1979). The amnion regulates movement of fetally-derived alpha-fetoprotein into maternal blood. *Journal of Laboratory and Clinical Medicine, 94*(2), 344-347.

7. Kelleher PC and Smith CJ (1979). Origin of maternal serum alpha-fetoprotein. *Lancet, 2*(8155), 1301-1302.

8. Bartha JL, Illanes S, Gonzalez-Bugatto F, Abdel-Fattah SA, Mizejewski GJ and Soothill PW (2007). Maternal serum transformed alpha-fetoprotein levels in women with intrauterine growth retardation. *Fetal Diagnosis and Therapy 22*(4), 294-298.

9. Gonzalez-Bugatto F, de Los Angeles-Ballen R, Bartha JL et al., (2009). Transformed alpha-fetoprotein (t-AFP) levels in women with threatened Preterm Labor. *Gynecologic and Obstetric Investigation, 68*(3), 199-204.

10. Gonzalez-Bugatto F, Foncubierta E and Bartha JL (2009). Maternal and fetal serum transformed alpha-fetoprotein levels in normal pregnancy. *Journal of Obstetrics and Gynecology Research, 35*(2), 271-276.