

# Association of Increased Second Trimester Serum Markers with Adverse Perinatal Outcome

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## Abstract

*Evidence has been inconsistent and at times conflicting with little data focusing on how predictive and effective serum alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG) as a marker of poor pregnancy outcome. In addition, no definite protocol has been developed on how to approach women found to have high level of serum AFP and hCG. The purpose of this study is to assess the association between the raised serum AFP on its own or combined with raised hCG with the adverse pregnancy outcome. At University Hospital Lewisham, all pregnant women are offered a second trimester quadruple test if they miss their first trimester screening due to late presentation. 281 women had raised serum AFP of >2 MoM and in 70 cases both serum AFP and beta-hCG were raised (>2MoM). The result of this study demonstrates that pregnancy complications were increased in women with unexplained abnormal quadruple screen analytes (high AFP and beta hCG levels of >2MoM). Although caution must be undertaken not to cause unnecessary anxiety, we feel that increased awareness and patient education could prevent certain pregnancy complications. Serum markers, in combination with other modalities such as ultrasound and Doppler, may improve detection rates of abnormal pregnancy outcomes.*

## Keywords

AFP, hCG, PET, IUGR

## I. Introduction

In the UK quadruple test is performed to screen Down's syndrome between 14 weeks + 2 days and 20 weeks + 0 days of gestation for those women who present late and missed first trimester screening test.

The quadruple test measure four maternal serum (MS) markers: alpha-fetoprotein (AFP), beta chorionic gonadotrophin (b-hCG), unconjugated oestriol (uE3), inhibin-A (inhibin). In pregnancies with Down's syndrome, AFP and uE3 levels tend to be low and b-hCG and inhibin levels tend to be raised. The level of AFP is also used to determine if there is an increased risk of spina bifida or anencephaly.

AFP is a 69-kDa single polypeptide fetal glycoprotein associated with both oncogenic and ontogenic growth [1]. It is synthesised in early gestation by the fetal yolk sac and then by the fetal liver. Its concentration reaches a peak at 13 weeks of gestation and then the decline. It is present in the fetal serum, passes into the fetal urine and then into the amniotic fluid. Finally AFP enters maternal circulation by diffusion across the placental membrane [2]. General belief is that AFP in the fetus has an analogous role to albumin in the adult. AFP is known to bind ligands such as fatty acids, steroids, bilirubin and heavy metals, and serves as a carrier/transport molecule [1]. AFP also increases growth. A disruption in the placental/fetal interface may allow increased diffusion of AFP into maternal serum, accounting for the increased levels [3]. There are two placental lesions associated with unexplained maternal serum AFP raise: chorionic villitis and vascular lesions of

infarction or thrombosis [4]. One study has shown that ischemic–thrombotic lesions in 88% of placentas were associated with elevated serum MS AFP levels [5]. Midtrimester amniotic fluid angiogenin levels have been shown to be significantly elevated in patients that had unexplained elevated MS AFP [6]. Hence angiogenin is a known marker of tissue ischemia, there may be a relationship between placental ischemia and elevated MS AFP levels.

HCG is a glycoprotein composed of 244 amino acids that is produced by the syncytiotrophoblast and maintains pregnancy by stimulating progesterone synthesis by the corpus luteum. A maximum level is reached by 10 weeks of gestation and declines as placental steroid synthesis starts [7]. Its alpha subunit is similar to luteinising hormone (LH), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH) and a beta subunit that is unique. Proteolytic cleavage by trophoblast macrophages destabilises the molecule, thereby producing free b-hCG that is secreted into the maternal circulation [1]. Second trimester low levels of hCG have not been linked to adverse outcomes, however, elevated hCG (>2–4 MoM) has been associated with multiple adverse outcomes [8]. The converse holds true for the first trimester, first trimester low levels of free b-hCG (<0.5 MoM) have been associated with low birthweight and increased risk of spontaneous miscarriage. First trimester elevations in free b-hCG have not been associated with any adverse obstetric outcome. Elevated levels of hCG in the second trimester may be attributed to hypoxia-induced cytotrophoblastic proliferation which has been documented in histological studies. Decreased perfusion to the

placenta may induce hypoxic changes, leading to cytotrophoblastic proliferation and subsequently to elevated levels of hCG [2]. It has been reported that large-for-gestational age placentas, a low fetoplacental weight ratio and retroplacental haematomas are more common in women with increased serum levels of hCG [9,15,16].

Several studies have investigated the correlation between the increased level of maternal serum alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG) and the adverse pregnancy outcome [10,11,12,13]. However, evidence has been inconsistent and at times conflicting with little data focusing on how predictive and effective these are as a marker of poor pregnancy outcome. In addition, no definite protocol has been developed on how to approach women found to have high level of serum AFP and hCG. The purpose of this study is to assess the association between the raised serum AFP on its own or combined with raised hCG with the adverse pregnancy outcome

## II. Methods

At University Hospital Lewisham, all pregnant women are offered a second trimester quadruple test if they miss their first trimester screening due to late presentation. Increased serum AFP and beta-hCG were detected in 300 cases of which 19 were excluded because of multiple pregnancies. 281 women had raised serum AFP of >2 MoM and in 70 cases both serum AFP and beta-hCG were raised (>2MoM).

Data collected from the patients' hospital notes, maternity patient database (Terranova software) and Astraia ultrasound database

(astraia software gmbh, Germany). Preterm birth, low birth-weight, severe pre-eclampsia, fetal or neonatal death, placental abruption and second trimester miscarriages are considered as adverse pregnancy outcomes. The proformas were collected and analysed using an Excel database.

Severe pre-eclampsia is defined as diastolic blood pressure of at least 110 mm Hg, or systolic blood pressure of at least 160 mm Hg, and/or biochemical and/or haematological impairment and/or symptoms. Severe IUGR (Intrauterine growth restriction) defined as fetuses needed to be delivered before 34 weeks of gestation due to abnormal arterial and venous Dopplers.

## III. Results

Results of 281 women with increased second trimester AFP levels; 10% (n=30) had severe preeclampsia, 8.5% (n=24) had severe IUGR, 17.5% (n=49) had preterm birth before 34 weeks gestation either spontaneous or iatrogenic and 7.8% (n=22) had placental abruption. Review of perinatal outcome showed 16.3% (n=46) admissions to SCBU/NICU, 1.4% (n=4) stillbirth, 7.8% (n=22) second trimester miscarriages and 5.6% (n=16) fetal structural abnormalities and one pregnancy was affected by Trisomy 18. For all outcomes, abnormalities of two analytes were more strongly associated with all adverse perinatal outcomes than any single marker alone, but numbers remain small for this subgroup (n=70). Of 281 women 31.9% (n=90) had emergency LSCS, 12.7% (n=35) had instrumental delivery.

#### IV. Discussion

The result of this study demonstrates that pregnancy complications were increased in women with unexplained abnormal quadruple screen analytes (high AFP and beta hCG levels of >2MoM). The optimal method to manage these pregnancies is unclear. Although caution must be undertaken not to cause unnecessary anxiety, we feel that increased awareness and patient education could prevent certain pregnancy complications. [14,17]. One recent study has shown that increased surveillance did not achieve earlier or improved detection rates of adverse events in comparison with routine antenatal care. We believe educating women about the signs and symptoms of pre-eclampsia, preterm labour, decreased fetal movements and vaginal bleeding may be of some value. It is argued that women with previous adverse outcome or medical conditions will automatically be subjected to higher surveillance, and therefore it is the low-risk pregnancy with unexplained values of first or second trimester serum analytes that are at the highest risk for complications [2].

#### V. Conclusion

There is little evidence to guide clinicians as to when, who and what type of increased surveillance is indicated, if any [18,19]. Serum markers, in combination with other modalities such as ultrasound and Doppler, may improve detection rates of abnormal pregnancy outcomes. It should be emphasised that the evidence is lacking as to whether any form of screening is beneficial for this group of patients.

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