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Unjustified abnormalities of analytes in the second trimester

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Abstract
There is a justified relationship between high levels of each of the hCG or dimeric inhibin alpha in the second trimester and the undesirable complications of pregnancy. The findings reported are similar to the findings that have to do with high levels of AFP, and they include: intrauterine growth restriction *(*IUGR*)*, Pre-eclampsia, Preterm birth, fetal death, and stillbirth. In addition, when some indicators are at a high level, the likelihood of undesirable result will increase. Combined screening increases aneuploidy diagnosis. For this very reason, for women seeking pregnancy cares in the first trimester. The major abnormalities and minor ultrasound markers are remarkably helpful in aneuploidy diagnosis. Except for a few cases, the risk of aneuploidy coincidence with the major abnormalities is so widespread that calls for conducting aggressive tests to determine fetal karyotype or chromosomal microarray. When a fetus is suffering from an abnormality, it is likely to suffer from other abnormalities as well. In spite of their significant effect on prognosis, the likelihood of their diagnosis by ultrasound is low or impossible. Most of the fetuses suffering from aneuploidies in which the intrauterine fetal death is high (such as 18 and 13 trisomy and tetraploidy) have abnormalities that are visible in the second trimester by applying ultrasound.

Keywords: analytes, second trimester, abnormalitie

Introduction
There is a justified relationship between high levels of each of the hCG or dimeric inhibin alpha in the second trimester and the undesirable complications of pregnancy. The findings reported are similar to the findings that have to do with high levels of AFP, and they include: intrauterine growth restriction (IUGR), Pre-eclampsia, Preterm birth, fetal death, and stillbirth. In addition, when some indicators are at a high level, the likelihood of undesirable result will increase [1]. However, the sensitivity and the positive predictive value of these markers are too low to be clinically proper for screening and pregnancy management [2]. Low levels of estriol in the mother's serum i.e. estriol levels lower than 0.25 MoM in the mother's serum have to do with to rare conditions yet significant.

1. Smith-Lemli-Opitz syndrome (SLOS)
It is an autosomal recessive state that is characterized by a mutation in the enzyme 7-Dehydrocholesterol reductase. This syndrome is likely to be associated with abnormalities in the central nervous system, heart, kidneys, important genital organs, and intrauterine growth restriction. The Society for Maternal-Fetal Medicine recommends that if the estriol level is lower than 0.25 MoM, Medical ultrasound (diagnostic sonography) needs to be conducted [3]. If abnormalities are identified, a high level of 7-dehydrocholesterol can be diagnosed and confirmed.

1. The lack of Steroid sulfate which is also called X-linked ichthyosis is likely to occur in the background of a syndrome of the neighboring genes. In these cases, this status is likely to be related to Kallmann syndrome, Chondrodysplasia punctate, or mental retardation [4]. If the estriol level is lower than 0.25 MoM and the fetus is male, it is likely to consider fluorescence in situ hybridization for investigating the status of steroid sulfate gene on X chromosome [5].

The combined screening of the first and second trimester
Combined screening increases aneuploidy diagnosis. For this very reason, for women seeking pregnancy cares in the first trimester, the American College of Obstetricians and Gynecologists (2013 c) recommends a strategy including first and second trimester screenings. There are three strategies for screening.

1. **Integrated Screening:** This method combines the results of the screening tests of the first and second trimester. This method includes the combination of fetal NT measurement and serum analyte levels in weeks 11-14 of pregnancy in addition to levels of quadral markers in weeks 15-20. Then, given these seven parameters, the aneuploidy risk is assessed. As it is expected, the integrated screening has the highest rate of Down syndrome diagnosis (diagnosis rate of 94-96%, false positive rate of 5%). If NT measurement is not possible, serum integrated screening is used for measuring the risk rate; serum integrated screening includes all six serum indicators. However, this method is less effective [6].
2. **Sequential Screening:** This method clarifies the result of first trimester screening in a high-risk women. Then, these women are recommended to conduct aggressive tests such as chorionic villus sampling (CVS) and amniocentesis [7]. In this method, there are two strategies:

a. In step-by-step sequential screening, women whose first trimester screening results indicate Down syndrome more than a definite threshold are recommended to conduct aggressive tests. Other women will conduct second trimester screening. The threshold level is defined at 1 percent; in a screened population, as many as 70% of the pregnancies suffering from Down syndrome occur at 1% of risk [8]. This screening method might achieve the diagnosis rate of 95%.
b. In conditional sequential screening, women are divided into high-risk, low-risk, and moderate risk groups. Individuals having the highest risk level (for example more than 1%), aggressive tests are recommended. In the moderate risk group (including 15-20% of the population), second trimester screening is conducted. As for the remaining 80-85% of the population (being at risk of lower than 1:1000), the screening result is reported to be negative, and they do not receive further tests [9]. Thus, most of the individuals that participate the screening process will receive the results immediately. However, the high rate of diagnosis is still maintained. The diagnosis rate ranges from 88 to 94%. This strategy is economical; by adopting this strategy, there will be no need for conducting the second trimester screening in 85% of the patients.

Integrated and sequential screening strategies call for the interaction between the patient and laboratory, so that it is made sure that the second sample has been take at an appropriate age of pregnancy and sent to the same laboratory. Moreover, in this way, a proper relationship is established between the screening results the first and second trimester [10].

Fetal extracellular DNA screening

By using massively parallel sequencing or chromosome-selective sequencing for separating the Fetal extracellular DNA from mother's serum, the diagnosis of Down syndrome and other fetal autosomal trisomies will be possible in week 10 of pregnancy. In the recent clinical trials of these techniques in high-risk pregnancy, the diagnosis rate of 21, 18, and 13 trisomies are approximately 98% (with the false positive rate of 5% or less [11]. More recently, this new technology has been clinically available as a screening test; however, it is not considered as an alternative diagnostic test. Conducting pretest counselling is recommended. If the result is diagnosed to be abnormal, conducting genetic counselling will be necessary, and for confirming the result, prenatal diagnosis tests need to be recommended. At present, the American College of Obstetricians and Gynecologists (2013 b) recommends this test to the following groups:

- Women who are 35 years old or more at the time of delivery;
- Women whose ultrasound results indicated their increased fetal aneuploidy risk;
- Women who has the history of trisomy 21/18/13-affected pregnancy;
- If the patient or her husband is a carrier of Robertson balanced displacement indicating the increased risk of embryo's suffering from trisomy 21 and 13.
- Individuals whose screening results of the first and second trimester or combined screening of the first and second trimester are abnormal in terms of aneuploidy.

The abovementioned college (the American College of Obstetricians and Gynecologists) does not recommend this test for low-risk women or women pregnant with multiple births (ACOG, 2012 b).

Ultrasound Screening

The major abnormalities and minor ultrasound markers are remarkably helpful in aneuploidy diagnosis. Except for a few cases, the risk of aneuploidy coincidence with the major abnormalities is so widespread that calls for conducting aggressive tests to determine fetal karyotype or chromosomal microarray. When a fetus is suffering from an abnormality, it is likely to suffer from other abnormalities as well. In spite of their significant effect on prognosis, the likelihood of their diagnosis by ultrasound is low or impossible. Most of the fetuses suffering from aneuploidies in which the intrauterine fetal death is high (such as 18 and 13 trisomy and tetraploidy) have abnormalities that are visible in the second trimester by applying ultrasound. However, only as many as 25-30% of fetuses suffering from Down syndrome have a major abnormality diagnosable by ultrasound in the second trimester [12].

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