

First and Second-Trimester Maternal Serum Analytes for the Prediction of Adverse Pregnancy Outcomes

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ABSTRACT

Background & Objective: Maternal serum levels of the first- and second-trimester markers for aneuploidy have been revealed to be associated with adverse pregnancy outcomes in the absence of neural tube defects or aneuploidy. This finding can guide clinicians for early diagnosis and management of such outcomes. However, previous findings are conflicting in this regard. Therefore, this study evaluated the detection of adverse pregnancy outcomes by first- and second-trimester serum screening analytes.

Materials & Methods: We prospectively recruited 972 females who underwent first and second-trimester aneuploidy screening. We gathered information on maternal demographic characteristics and serum biomarkers (free B-hCG and PAPP-A for the first-trimester; AFP, B-hCG, Inhibin-A, and unconjugated estradiol for second-trimester). At the end of the study, adverse pregnancy outcome was recorded.

Results: Abnormal screening results were reported in 34 (3.5%) patients. Two groups were significantly different in maternal age, BMI, and gestational period ($P=0.017$, 0.003 and 0.021 , respectively). Among the measured adverse outcomes, preeclampsia was significantly more prevalent in the case group ($P<0.0001$). Abnormal levels of Inhibin-A is associated with the incidence of preeclampsia (RR: 29.87, CI: 13.22-67.49, $P<0.0001$). Additionally, patients with an abnormal level of Inhibin-A had a shorter gestational period (255.5 ± 24.53 vs. 264.79 ± 8.99 , $P=0.006$). Likewise, patients with an abnormal level of maternal serum alpha-fetoprotein (MSAFP) had a shorter gestational period (252.0 ± 29.3 vs. 264.8 ± 8.93 , $P=0.001$).

Conclusion: First- and second-trimester maternal serum biomarkers could provide a possible screening tool for early detection of preeclampsia.

Keywords: Pregnancy complications, Maternal serum markers, Pregnancy



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Introduction

The dawn of prenatal screening was initiated by measuring alpha-fetoprotein in the second trimester of pregnancy to recognize neural tube defects (1, 2). Through the decades, the field of prenatal screening has advanced thus far that biochemical markers and ultrasonography are implemented to detect at-risk patients for open neural tube defects, trisomy 18/13, and Down syndrome throughout the pregnancy (3, 4). Recently, prenatal screening has been investigated to a new practice. Numerous reports concerning the efficacy of prenatal screening to identify high-risk pregnancies for other adverse outcomes during the perinatal period have been published (5-11), which has led to several reviews and consensus opinions (5, 12-19). These tests are performed early in the course of pregnancy; thus, early detection of maternal disease

can be provided with the potential to reduce morbidity and mortality (3, 20). For example, a meta-analysis has shown a slight therapeutic efficacy of aspirin on decreasing the incidence of preeclampsia (21). However, the re-analysis of those studies included in the first meta-analysis indicated that aspirin administration prior to 16 weeks reduces the incidence of preeclampsia to 53% (22-24). Also, by confining the analysis to early-onset preeclampsia, the incidence drops approximately 90% (22). Moreover, the study indicated that aspirin administration in the first four months of pregnancy was effective in decreasing fetal growth restriction, fetal death, placental abruption, antepartum hemorrhage, and preterm birth (22, 25, 26). Other interventions, such as progesterone or cervical cerclage, have been reported effective for the

prevention of preterm birth (27). Furthermore, fetal surgery is currently a viable option for the treatment of myelomeningocele (28). Lastly, early detection of placental disorders can prepare the medical team for potential complications during delivery (29, 30).

The aim of this cohort study was to evaluate the role of double (first-trimester) and quadruple (second-trimester) screening tests, which are currently employed for detection of aneuploidy to elucidate any further advantage in detecting other conditions beyond the primary intention of use.

Materials and Methods

This prospective cohort study was conducted during 2017-2018 at Imam Khomeini University Hospital in Sari, Iran. Patients with a maternal age more than 35 years and a previous history of intrauterine growth restriction (IUGR), preeclampsia, known genetic disease, abnormal amniocentesis, autoimmune diseases, diabetes including gestational diabetes mellitus (GDM), and thyroid diseases excluded from the study. Only subjects with singleton gestations were included in this study. Initial demographical and clinical data were obtained from the database of our institute. Age, BMI, gravidity, parity, family history, gestational age, previous pregnancy, and fetal outcomes were extracted from the database. Gestational age was predicted based on early pregnancy ultrasonographic evaluation. First-trimester double screening, including free beta human chorionic gonadotropin (fB-hCG) and pregnancy-associated plasma protein A (PAPP-A) was measured between 11 and 13 weeks of gestation. Alpha fetoprotein (AFP), unconjugated estriol, B-hCG, and Inhibin-A measured as the second-trimester quadruple screening test at 15 to 18 weeks of pregnancy. The first-trimester risk was predicted based on measurements of nuchal translucency and two serum markers, together with maternal age. The second-trimester risk was calculated from measurements quadruple test, along with maternal age. Ultrasonographic examinations for nuchal translucency were performed by an experienced radiologist in the 11–13 weeks. Also, a certified maternal-fetal medicine specialist reviewed all images. Abnormal levels of serum analytes were defined as follows: AFP, B-HCG, and Inhibin-A MoM value < 2, and PAPP-A and unconjugated estradiol > 0.5 MoM value.

Based on screening data, patients were clustered into two groups. The case group with an abnormal screening test, and the control group with a normal screening test. Subsequently, patients were followed until delivery. Patients were followed regularly by the outpatient unit of the obstetrics department.

Table 1. Demographic characteristics of two cohort groups

At the end of the study, the incidence of maternal and fetal conditions, such as preeclampsia, premature rupture of membrane (PROM), placental abruption, abortion, placenta previa, intrauterine fetal death (IUFD), still death, IUGR, aneuploidy, preterm birth, small for gestational age (SGA), large for gestational age (LGA), hydrops fetalis, low birth weight, and organ malformations were documented.

Preeclampsia was defined as blood pressure >140 mm Hg systolic and/or 90 mm Hg diastolic on two or more occasions, with at least 4 hours apart with proteinuria of 300 milligrams or more in a 24-h urine specimen or 1+ or higher on random urine dipstick occurring after 20 weeks' gestation in a woman with previously normal blood pressure (31). Preterm labor was defined as birth earlier than 37th weeks of gestation, SGA was defined as fetal age lower than two standard deviations or <10th percentile according to gestational age and normal population. Low birth weight was defined as lower than 2500gr upon birth or <10th percentile according to gestational age.

For data analysis, SPSS version 18.0 (SPSS Inc., Chicago, Ill., USA) was used. Qualitative and quantitative variables were expressed as frequencies and mean \pm standard deviation, respectively. Relative risk (RR) and confidence intervals were employed to express the magnitude of difference. Chi-square and Fisher's exact tests were used for qualitative variables. Independent t-test was employed for quantitative variables. P-value<0.05 was considered as statistically significant.

Results

Among 1,022 patients in the present cohort study, outcome data of 972 (95%) cases were available. The abnormal screening results were reported in 34 (3.5%) patients. In addition, 12 patients had abnormal maternal serum alpha-fetoprotein (MSAFP), four patients had abnormal fBhCG, four patients had abnormal unconjugated estriol, and 16 patients had abnormal Inhibin-A. The demographic characteristics of our two cohort groups and the adverse outcomes are shown in [Table 1](#) and [Table 2](#), respectively. Evaluating the association between individual test and pregnancy outcome revealed that elevated levels of Inhibin-A is associated with the incidence of preeclampsia (RR: 29.87, CI: 13.22-67.49, $P<0.0001$). Additionally, patients with an abnormal level of Inhibin-A had a shorter gestational period (255.5 ± 24.53 vs. 264.79 ± 8.99 , $P=0.006$). Likewise, patients with an abnormal level of MSAFP had a shorter gestational period (252.0 ± 29.3 vs. 264.8 ± 8.93 , $P=0.001$).

Demographic	Control group (n= 938)	Case group (n= 34)	P-value
Maternal age (years)	28.12 ± 4.53	30.82 ± 5.22	0.017
BMI (kg/m ²)	26.18 ± 3.82	29.1 ± 4.58	0.003
Previous history of abortion	202 (21.5)	8 (23.5)	0.844
Familial history of neonatal abnormality	0	122 (13)	0.112
Gestation (days)	264.83 ± 9.02	259.41 ± 17.4	0.021

Data are expressed as Meas ± SD
Percents are expressed in parenthesis

Table 2. Comparison of adverse outcomes between two cohort groups

Adverse outcome	Control group (n= 938)	Case group (n= 34)	Relative risk (CI 95%)	P-value
Low birth weight	26 (2.8)	2 (5.9)	-	0.479
Pre-eclampsia	16 (1.7)	14 (41.2)	24.14 (9.89-58.87)	< 0.0001
Preterm labor	42 (4.5)	2 (5.9)	-	0.784
PROM	16 (1.7)	2 (5.9)	-	0.21
Total	72 (7.7)	16 (47.1)	6.13 (3.38-11.1)	< 0.0001

Percents are expressed in parathesis.

Discussion

In this study, maternal first-trimester (double) and second-trimester (quadruple) tests were used as the screening tools for aneuploidy (32, 33). Additionally, MSAFP was used to screen ventral wall and neural tube defects, which has been widely replaced by the introduction of more advanced ultrasonographic evaluation for first- and second-trimester fetal anatomical anomalies (34-36). We designed a prospective cohort study to explore the role of abnormal maternal first- and second-trimester double and quadruple tests in diagnosing adverse pregnancy outcomes. During our cohort study, 486 pregnant subjects underwent routine double and quadruple aneuploidy screenings at Imam Khomeini University hospital of Sari, Iran.

We found a 3% prevalence of preeclampsia, which is consistent with the reported epidemiologic data available in the literature (37).

Yazdani *et al.* conducted a historical cohort in 2012-13. They evaluated 231 pregnant subjects with a quadruple screening test in 14-18 weeks of gestation and found a significant association between abnormal quadruple test and adverse pregnancy outcomes such as PROM, preeclampsia, and fetal growth restriction (38). Nevertheless, in a similar study conducted by Feizbakhsh *et al.*, no significant association was established between the placental abruption, intrauterine fetal death (IUFD), preeclampsia, and preterm labor with the triple screening test (39).

In our study, adverse pregnancy outcomes including, preterm labor, PROM, preeclampsia, and low birth weight were investigated, and our results indicated that preeclampsia had a significant increase compared to the control cohort group. However, no significant

association between abnormal double or quadruple tests with preterm labor, low birth weight, and PROM was established. According to our results, an abnormal screening test elevates the risk of preeclampsia in pregnancy by 24.14 times. Moreover, an abnormal screening test was associated with 6.13 times more negative pregnancy outcomes in general. However, abnormal screening tests were not associated with low birth weight and PROM. Abnormal Inhibin-A and MSAFP were associated with a significantly shorter gestational period.

Additionally, it has been shown that the abnormal Inhibin test is positively correlated with preeclampsia (RR: 29.87). Our results were consistent with existing reports on the elevation of preeclampsia in individuals with abnormal Inhibin-A levels (40-43). However, Fayazbakhsh *et al.* reported no significant correlation between abnormal Inhibin-A and preeclampsia (39).

Several biochemical markers such as fB-HCG, MSAFP, PAPP, placental B-protein, CRH, and Activin-A have been considered to predict or evaluate the progress of preeclampsia (15-17, 19). Inhibin is a glycoprotein hormone and member of the transforming growth factor superfamily consisting of alpha-beta A (inhibin A) and alpha-beta B (inhibin B). During pregnancy, the corpus luteum is a major source of Inhibin. The latest studies have shown the placenta-fetal unit as the origin of Inhibin A (44). Inhibin A level is considerably higher during pregnancy. In early pregnancy (8-13 weeks and 15-19 weeks), Inhibin A levels decrease, and then increase till the peak is reached at the 37th week of gestation (40).

Our study suggested that first-trimester double test and second-trimester quadruple test can predict

preeclampsia in pregnant women. Moreover, this study was performed in a large unselected population receiving routine clinical care, which supports the idea that screening for preeclampsia is feasible during early pregnancy without any additional risk or cost.

The main limitations of this study include its small case group population and significantly different demographic characteristics between groups. Additional analysis of the association of individual serum analytes and adverse pregnancy outcomes was also impeded due to our relatively small sample size. We planned to record many other adverse outcomes such as abortion, placenta previa, placental abruption, intrauterine fetal death, hydrops fetalis, and congenital malformations, but none appeared in our selected population. We did not evaluate the associated parameters of adverse outcomes in pregnancy, such as uterine artery doppler indices and maternal mean arterial pressure. Therefore, our model could be more applicable in settings that have similar limitations to ours. Moreover, in the case of delivery outside of our hospital, the diagnosis of preeclampsia was acquired from a referring provider's office or patient self-report.

Conclusion

Our results indicated that abnormal double and quadruple tests in the first and second trimesters can be helpful in the prediction of preeclampsia. Furthermore, abnormal PAPP-A levels alone provide an effective screening tool for the prediction of preeclampsia.

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Conflict of Interest

Authors declared no conflict of interests.

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Ethical Approval

The study was approved by the Ethical Committee of Mazandaran University of Medical Sciences. The study was conducted under ethical committee's supervision. After briefing about the study, Informed verbal and written consent was obtained from individual study participants. Patients who declined to participate in the study received best medical care

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