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Original Article

Comparison of pregnancy outcomes in amniocentesis recipients with normal and abnormal maternal serum analytes

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Abstract

Considering the relatively high frequency of genetic disorders associated with negative pregnancy outcomes, in this research, adverse pregnancy outcomes in amniocentesis patients were compared between two groups with normal and abnormal maternal serum analytes. This retrospective cohort study was conducted on singleton pregnant women who underwent amniocentesis and had fetuses with normal chromosomes at the perinatology clinic in Rasht. Eligible patients were divided into two groups of 307 people with normal and abnormal maternal serum analytes based on laboratory screening results. Adverse pregnancy outcomes were compared between the two groups. In a total of 614 pregnant women, adverse pregnancy outcomes were observed in 24% of the abnormal analyte group and 15% of cases in the normal analyte group. The association between adverse pregnancy outcomes and both normal and abnormal analytes was found to be statistically significant ($p<0.05$). the most common adverse pregnancy outcome was hypertensive disorders, which was more prevalent in the abnormal analyte group (10.7%). The presence of abnormal levels of free beta-human chorionic gonadotropin (free β-hCG) and inhibin-A factors were found to be associated with adverse pregnancy outcomes. Specifically, for each unit increase in inhibin-A level, the likelihood of experiencing an adverse pregnancy outcome was reported to be 1.83 times higher (OR=1.83, P=0.028). Similarly, the presence of abnormal free β-hCG values was associated with a 3.12 times higher chance of adverse pregnancy outcomes (OR=3.115, P=0.03). The utilization of serum analytes for first and second-trimester screening can be beneficial in the prediction of adverse pregnancy outcomes, particularly hypertensive disorders during pregnancy.

Keywords: Amniocentesis, Maternal serum analytes, Outcome, Pregnancy

1. Introduction

Pregnancy represents a critical phase in the women's lives, where the mother's health significantly impacts the well-being of the fetus and the newborn. The presence of preexisting conditions, diseases, or disorders developed during pregnancy, along with external factors, can pose a threat to the health of the mother, the fetus, or both [1]. Factors such as pre-eclampsia, hypertension, and gestational diabetes, as well as premature birth, macrosomia, and low birth weight (LBW), pose significant risks to both the mother and the newborn's health [2]. Conversely, a child born with genetic abnormalities such as Down syndrome can pose numerous challenges for the individual, their family, and the wider community [3]. Approximately 3% of infants face the peril of disability and mortality due to congenital abnormalities and genetic disorders [4]. Genetic disorders may manifest either at birth or later in life. These disorders can impact various aspects of development, like Down Syndrome, or result in physical symptoms like muscular dystrophy. In certain cases, such as Huntington's disease, symptoms may not present themselves until adulthood [3]. Hence, any earnest endeavor to ascertain the influential factors contributing to the occurrence of congenital abnormalities and their subsequent prevention will result in a healthier and improved future generation, while also averting the occurrence of devastating societal consequences [5]. Screening tests have effectively diminished the necessity for prenatal genetic testing, thereby mitigating the likelihood of miscarriage and alleviating the financial burden associated with the test [6]. In cases where the screening outcome indicates high risk and is positive, a conclusive diagnosis requires implementing procedures such as chorionic villus sampling (CVS) and amniocentesis (sampling of amniotic fluid) [7]. Amniocentesis, a prenatal genetic testing procedure, is typically conducted during the 15th to 17th week of pregnancy. Performing this procedure before the 15th week has been linked to an increased risk of fetal loss and other complications, including cell culture failure [8]. Furthermore, the amniocentesis procedure has the potential to give rise to various

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complications, including the rupture of the amniotic sac, infection, chorioamnionitis, fetal demise within the uterus, and termination of pregnancy [9, 10]. Nevertheless, it is favored in comparison to the CVS test due to the increased likelihood of unwanted abortion [7]. Suppose the maternal serum analyte screening tests indicate a high risk of the fetus developing Down syndrome. In that case, it is advisable to proceed with fetal sampling (amniocentesis or CVS chorionic villus sampling) to conduct a karyotype genetic diagnosis test [11]. Several studies have reported on the association between levels of maternal serum markers and various pregnancy outcomes, including preterm delivery, fetal growth disorders, hypertensive disorders, and spontaneous abortion [12]. Abnormal levels of pregnancy-associated plasma protein-A (PAPP-A) or human chorionic gonadotropin (hCG) in high-risk women are linked with unfavorable pregnancy outcomes. This association can be utilized as a tool to identify women who would benefit from additional monitoring during their pregnancy [13]. Further investigation is required to ascertain whether the implementation of monitoring and intervention protocols can enhance the outcomes of pregnancies in cases where abnormal markers are detected [14]. Furthermore, it is crucial to consider the potential ramifications of pregnancy in individuals who have undergone amniocentesis. Can the analytes effectively ascertain the prognosis and forecast the outcomes of pregnancy? Consequently, this study aimed to evaluate and compare the pregnancy outcomes of amniocentesis patients with both normal and abnormal maternal serum analytes.

2. Materials and methods

2.1. Retrospective Cohort Study on Singleton Pregnant Females Undergoing Second Trimester Amniocentesis: Exclusion Criteria and Focus on Normal Chromosomal Patterns

This is a retrospective cohort study that was carried out on singleton pregnant females who sought consultation at the perinatology clinic in Rasht City. These women underwent amniocentesis, and it was confirmed that their fetuses had normal chromosomal patterns. The study specifically focused on mothers who underwent amniocentesis during the second trimester of their pregnancy and also underwent screening either in the first or second trimester. The study excluded women who had pre-pregnancy diabetes, heart, liver, kidney, and rheumatological diseases, multiple pregnancies, structural or chromosomal defects, pregnancies resulting from in-vitro fertilisation (IVF), and a history of repeated or second 3-month miscarriage, intrauterine fetal demise (IUFD), preterm delivery, intrauterine growth restrictions, rupture of the amniotic sac, hypertensive disorders, oligohydramnios, low birth weight in previous pregnancies, patients with nuchal translucency (NT) ≥ 3, and patients with neural tube defect (NTD) risk factors. These cases were considered to have a higher risk of unfavorable consequences during pregnancy and were therefore not included in the study. The exclusion criteria also involved the inability to monitor pregnancy complications and the patient's lack of cooperation in providing information.

2.2. Sample Size Determination for Comparing Adverse Pregnancy Outcomes

To determine the sample size needed to compare adverse pregnancy outcomes between two groups with normal and abnormal analytes, the researchers used a formula based on the study conducted by Barrett et al. [15]. They considered a 95% confidence level and 80% test power. Additionally, to account for the longitudinal nature of the study and the possibility of loss to follow-up, 15% was added to each group. This calculation resulted in an estimated sample size of 355 individuals in each group. Ultimately, the study included 614 people in one group and 307 people in the other group.

$$n_1 = n_2 = \frac{(p_1(1-p_1) + p_2(1-p_2))(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{(p_1 - p_2)^2}$$

All patients underwent a screening test during both the first and second trimesters. Following approval from the ethics committee of Guilan University of Medical Sciences (Ethical code: IR.GUMS.REC.1399.590), patients were divided into two groups: those with negative screening results and normal analyte levels, and those with positive screening results or abnormal analyte levels. Patients who tested negative on the laboratory screening and had all analytes within the normal range were categorized together based on additional factors such as patient preference, advanced maternal age, history of genetic abnormalities in prior pregnancies, or familial genetic conditions, and subsequently underwent amniocentesis. Conversely, patients with positive screening results on the laboratory screen or with any analytes falling outside the normal range were assigned to a separate group.

Data recorded includes information on various factors such as age, number of pregnancies, body mass index (BMI), gestational age at the time of amniocentesis, results of screening tests, and determination of values based on multiples of the median (MOM). Additionally, current pregnancy outcomes are documented, including birth weight (LBW: less than 2500 grams), amniotic fluid leakage or rupture of the water sac before the onset of labor pains, preterm birth (birth before 37 weeks), neonatal intensive care unit (NICU) admissions, miscarriage (pregnancy loss before 20 weeks), intrauterine fetal death (death of the fetus inside the womb after 20 weeks), and neonatal death (death of the baby up to 28 days after birth). Furthermore, the presence of hypertensive disorders in pregnancy is also recorded, which includes pregnancy-induced hypertension (onset of high blood pressure after 20 weeks of gestation without proteinuria or organ dysfunction) and pre-eclampsia (onset of hypertension, proteinuria, or organ dysfunction after 20 weeks of pregnancy). Lastly, intrauterine growth restriction (weight percentile less than 10% for gestational age) is documented[16, 17].

The serum markers' concentration is evaluated in MoM, with specific cut-off points utilized as outlined. During the initial trimester, PAPPA levels below 0.4, free β-hCG levels below 0.5 or above 2, and in the second trimester AFP levels below 0.25 or above 2.5 were deemed significant. HCG levels exceeding 3, UE3 levels below 0.5, and INHIBIN-A levels surpassing 2 were classified as abnormal.

First trimester: PAPP-A (<0.4 MoM) (14), free β-hCG (<0.5MoM)(14) or >2 (18); Second trimester: AFP (<0.25 (14) or >2.5 MoM (14, 18), β-hCG (.>3 MoM) (14), UE3 (<0.5 MoM) (14), Inhibin A(.>2MOM)(19).

The study examined the incidence of negative pre-

gnancy outcomes among individuals who underwent amniocentesis, comparing two cohorts based on the results of their screening tests. Furthermore, an analysis was conducted to explore the correlation between adverse pregnancy outcomes and the screening tests administered.

2.3. Statistical analysis

The data collected for this study underwent coding and were subsequently inputted into SPSS 21 software. Qualitative data were described using frequency and percentage, while quantitative data were analyzed using measures such as mean, median, and standard deviation. Additionally, various statistical tests including the chi-square test, Fisher's exact test, and Mann-Whitney test were employed to compare between two groups during the data analysis phase. To determine the odds ratio and identify independent risk factors while controlling for the effects of demographic and clinical variables, both crude and adjusted logistic regression models were utilized. The statistical significance level for all tests was set at P<0.05.

3. Results

3.1. Demographic Characteristics and Pregnancy Outcomes in Pregnant Women Undergoing Amniocentesis

The information gathered from 614 pregnant women who underwent amniocentesis was divided into two groups based on their analyte levels: normal (307 individuals) and abnormal (307 individuals). The demographic characteristics of the patients in each group are presented in Table 1. The mean age of the participants in the normal analyte group was 33.2 ± 4.9 years, with an age range of 20-47 years. In contrast, the mean age of those in the abnormal analyte group was 32.9 ± 5.5 years, with an age range of 16-44 years. There was no statistically significant difference in age between the two groups. However, patients with normal analyte levels had significantly higher average gestational age and baby weight (P < 0.05). Adverse pregnancy outcomes were experienced by 19.7% (121 individuals) of the patients, while 80.3% (493 individuals) had no adverse events. These outcomes included miscarriage (0.3%), infant death (0.6%), IUFD (0.5%), premature rupture of membranes (2.5%), hypertensive disorders (8%), preterm birth (9.9%), small for gestational age (SGA) (6.7%), low birth weight (6.4%), and admission to the NICU (3.6%). The most common adverse outcome observed was related to hypertensive disorders (Figure 1).

3.2. Association Between Analyte Levels and Adverse Pregnancy Outcomes

Based on the findings of the chi-square test, a statistically significant association was observed between adverse pregnancy outcomes and both normal and abnormal analytes (p <0.05). Patients with abnormal analytes had a higher incidence of adverse pregnancy outcomes, with a rate of 24.1% (Table 2).

3.3. Association of Analyte Levels with Hypertensive Disorders in Pregnant Women

Comparing the pregnancy outcomes of the two groups, the chi-square test results indicated a significant disparity in hypertensive disorders (P=0.011) between the groups. It was observed that the incidence of hypertensive disorders was higher in the abnormal analyte group (Table 3).

3.4. Impact of Inhibin-A and Free-βhcg-Group on Adverse Pregnancy Outcomes

Multiple logistic regression was employed to control the impact of variables on pregnancy outcomes. The variables included in the model were BMI, inhibin-A, bhcg, free-bhcg-group, and PAPP-A, with a p-value less than 0.2. The findings of the logistic regression using the Backward

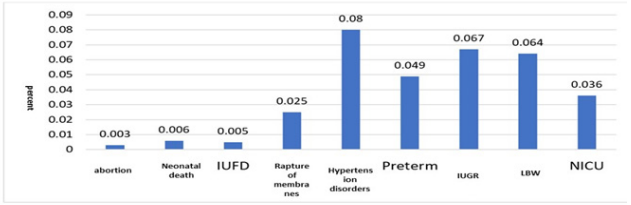

Fig. 1. The adverse pregnancy outcomes rate in amniocentesis patients. IUFD: Intrauterine Fetal Demise, IUGR: Intrauterine Growth Restriction, LBW: Low Birth Weight, NICU: Neonatal Intensive Care Unit.

Table 1. Mean/ median of demographic factors in amniocentesis patients in two groups.

Variable	Normal analytes			Abnormal analytes			
	Mean	Median	SD	Mean	Median	SD	P-value
Age	33.2	33.2	4.9	32.9	34	5.59	0.812
Parity	1.95	2	0.701	1.89	2	0.74	0.258
Gestational age(weeks)	17	17	1.9	16.4	16	1.7	<0.001 *
Maternal BMI	27.1	27.1	4.2	27.1	27	4.7	0.847
Neonatal weight (gram)	3360.1	3360.1	455.3	3232.8	3250	499.8	0.001 *

*Significant for <0.05, BMI: Body Mass Index.

Table 2. Frequency of adverse pregnancy outcomes in amniocentesis patients based on groups.

Pregnancy outcome	Normal analytes		Abnormal analytes		P- value
	Number	Percent(%)	Number	Percent(%)	
No	260	87.7	233	75.9	0.006 *
Yes	47	15.3	74	24.1	

*Significant for <0.05.

Table 3. Frequency of outcomes in amniocentesis patients based on groups.

Outcomes	Level	Normal analytes		Abnormal analytes		P-value
		Number	Percent (%)	Number	Percent (%)	
Abortion	No	306	99.7	306	99.7	0.999
	Yes	1	0.3	1	0.3	
IUFD	No	306	99.7	306	99.7	0.999
	Yes	1	0.3	1	0.3	
Death	No	305	99.3	305	99.3	0999
	Yes	2	0.7	2	0.7	
Rapture of membranes	No	302	98.4	297	96.7	0.191
	Yes	5	1.6	10	3.3	
Preterm birth	No	297	96.7	287	93.5	0.061
	Yes	10	3.3	20	5.6	
IUGR	No	292	95.1	281	91.5	0.075
	Yes	15	4.9	26	8.5	
LBW	No	291	94.8	284	92.5	0.321
	Yes	16	5.2	23	7.5	
Hypertensive disorders	No	291	94.8	274	89.3	0.011*
	Yes	16	5.2	33	10.7	
NICU	No	298	97.1	294	95.8	0.385
	Yes	9	2.9	13	4.2	

*Significant for<0.05, IUFD: Intrauterine Fetal Demise, IUGR: Intrauterine Growth Restriction, LBW: Low Birth Weight, NICU: Neonatal Intensive Care Unit

Table 4. The results of univariate logistic regression in investigating the effect of the studied variables on the adverse outcome.

Variable	*β*	SD	Parent statistics	P-value	OR Adj	OR (95% confidence interval)	
					Adjusted odds ratio	Lower limit	Upper limit
PAPP- A	- 0.906	0.513	3.117	0.077	0.404	0.148	1.105
Free- β.hcg- group (1)	1.136	0.523	4.728	*0.030	3.115	1.119	8.674
Inhibin- A	0.604	0.276	4.798	0.028*	1.830	1.066	3.141
Constant	- 2.033	0.665	9.334	*0.002	0.131	-	-

*Significant for<0.05, PAPP-A: Pregnancy Associated Plasma Protein-A.

method are presented in Table 4. The outcomes revealed that both the free-βhcg-group and inhibin-A factors had a significant influence on adverse pregnancy outcomes. Specifically, for each unit increase in inhibin-A level, while holding other variables constant, the likelihood of adverse pregnancy outcome was found to be 1.83 times higher (OR = 1.83, P = 0.028). Moreover, due to the non-normal distribution of free-β.hcg values, under the same conditions as the other variables, the chance of adverse pregnancy outcome was reported to be 3.12 times higher (OR = 3.115, P = 0.030).

4. Discussion

In this study, the researchers aimed to examine the occurrence of adverse pregnancy outcomes among patients who underwent amniocentesis, based on their maternal serum analyte levels. The findings of this investigation revealed that 19.7% of the patients experienced adverse pregnancy outcomes. Furthermore, it was observed that among patients with abnormal analyte levels or positive screening results, 24.1% experienced adverse pregnancy outcomes. On the other hand, among patients with normal analyte levels and negative screening results, 15.3% experienced adverse pregnancy outcomes. Previous research has demonstrated that women who tested positive during screening exhibited an increased likelihood of experiencing preeclampsia, placenta previa, and miscarriage before reaching the 20-week mark of their pregnancy [20]. The predominant finding in our research pertained to hypertensive disorders. A study conducted by Gomes et al in 2017 revealed that maternal serum marker levels were linked to negative pregnancy consequences such as preterm birth, fetal growth abnormalities, hypertension issues, and miscarriage[12]. In the current investigation, the findings from the univariate analysis of the outcomes indicated a higher incidence of preterm delivery and fetal growth restriction in the group with abnormal analyte levels. However, these results did not reach statistical significance. It is plausible that with a larger sample size, more substantial and noteworthy results could have been obtained. Singnoi et al. (2019) found a strong correlation between elevated inhibin A levels and a heightened likelihood of developing

FGR, preeclampsia, and preterm delivery[18]. The current investigation revealed that the inhibin-A factor significantly impacted adverse pregnancy outcomes, as indicated by the results of multiple logistic regression analysis. Specifically, for every incremental unit rise in inhibin-A levels within the context of the other variables in the model, the likelihood of adverse pregnancy outcomes increased by a factor of 1.83 (OR = 1.83, P = 0.028). Rosner et al. (2015) carried out a research study to investigate the potential correlation between first and second-trimester biochemical markers of aneuploidy and adverse pregnancy outcomes in twin pregnancies. The study compared adverse pregnancy outcomes in patients with abnormal analytes to those with normal analytes. It was observed that patients with elevated inhibin A levels before 37 weeks of gestation had a higher likelihood of experiencing spontaneous delivery. The researchers also discovered that certain abnormal aneuploidy markers were linked to a heightened risk of adverse pregnancy outcomes in twin pregnancies[21].

According to additional discoveries from the current research, the outcomes of multiple logistic regression analysis indicated that the free β-hCG factor significantly influenced the outcome of pregnancy. Due to the non-normal distribution of free β-hCG values under similar circumstances as other variables, the likelihood of experiencing an adverse pregnancy outcome was found to be 3.12 times higher (OR = 3.115, P = 0.03). Godbole et al.(2016) conducted a retrospective study to assess the significance of maternal serum screening for fetal chromosomal aneuploidy in predicting adverse pregnancy outcomes. The study findings indicated that abnormal hCG levels in high-risk women could potentially serve as an indicator for identifying those who may benefit from additional monitoring due to the potential consequences of adverse pregnancy outcomes[22]. According to a study conducted by Rosner et al. (2015), an elevation in hCG levels during the second trimester of pregnancy was found to be linked with a higher likelihood of spontaneous delivery before 28 weeks gestation and the need for admission to the NICU[20]. Additionally, following prior research, elevated AFP concentrations have been linked to negative pregnancy results[23, 24]. In the research conducted by Rosner et al.(2015), the focus was on examining the correlation between first and second-trimester biochemical markers of aneuploidy and adverse pregnancy outcomes in both patients with normal and abnormal analytes, as well as in twin pregnancies. The findings indicated that individuals with elevated AFP levels had a greater likelihood of NICU admission. Furthermore, it was discovered that certain abnormal aneuploidy markers were linked to a heightened risk of negative pregnancy outcomes in cases of twin pregnancies[20]. The current investigation found that the AFP factor did not have a notable impact on pregnancy outcomes. The NICU admission rate was higher at 2.4% in the abnormal analyte group, however, the findings did not show a significant difference between the normal and abnormal analyte groups.

In a study conducted by Harper et al. in 2012, pregnant women who underwent either amniocentesis or CVS were examined. The main objective of the study was to determine the occurrence of fetal loss before reaching 24 weeks of pregnancy. The participants were divided into two groups: obese patients with a body mass index (BMI) of 30 or higher, and non-obese patients with a BMI lower than 30. The results of the study indicated that there was no significant difference in the risk of fetal loss before 24 weeks of gestation between obese women (2,742) and non-obese women (8,037) who underwent amniocentesis. The fetal loss rates were 4.7% for obese women and 4.2% for non-obese women. The adjusted odds ratio (OR) was 1/1, suggesting that there was no increased risk associated with obesity in this context. Similarly, for women who underwent CVS, no significant difference in the risk of pregnancy loss was observed between obese women (n=855) and non-obese women (n=4125). The fetal loss rates were 6.4% for obese women and 6.3% for non-obese women. The adjusted odds ratio was 1.0, indicating that obesity did not contribute to an elevated risk of pregnancy loss in this group. However, it is worth noting that higher rates of fetal loss were observed in cases of obesity class III (BMI 40 or higher) specifically for amniocentesis procedures[24]. However, in the present study, the BMI factor had no significant effect on adverse pregnancy outcome.

5. Conclusion

The findings of the research indicated that hypertensive disorders were the most prevalent adverse pregnancy outcome, particularly evident in the abnormal analyte group. Adverse pregnancy outcomes, such as preterm birth, fetal growth restriction, and low birth weight, were more frequently observed in the abnormal analyte group. Although the results did not reach statistical significance, they hold clinical relevance. Pregnant individuals with abnormal free β-hCG and elevated levels of inhibin-A face an increased risk of adverse pregnancy outcomes. Utilizing serum analytes for first and second-trimester screening can aid in the prediction of adverse pregnancy outcomes, particularly hypertensive disorders during pregnancy. Early identification of high-risk patients, coupled with enhanced monitoring and management strategies like uterine artery Doppler ultrasound, fetal growth assessment, and aspirin administration, may potentially mitigate fetal and maternal complications.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

The ethics committee of Guilan University of Medical Sciences approved the survey (IR.GUMS.REC.1399.590). All cases filled the written informed consent before the study begins.

Informed Consent

Informed consent was taken from all participants.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

Forozan Milani and Seyedeh Shahed Shoarishoar contributed to conception, research design and supervision; Sa-

mira Adineh and Zahra Rafiei Sorouri contributed to data acquisition, analysis, and interpretation; Seyedeh Maryam Attari and Forozan Milani drafted the manuscript. All authors read and approved the final version.

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Transparency Statement
All the authors affirm the honesty of all data this study.

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