Original Article

Is pregnancy associated plasma protein-A (PAPP-A) a marker for adverse perinatal outcomes in preterm isolated oligohydramnios cases?

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A B S T R A C T

Objective: Isolated oligohydramnios is defined as an amniotic fluid index below five centimeter with no other coexisting condition. There are still controversies about the management and pregnancy outcomes. A marker predicting these is crucial. Low pregnancy associated plasma protein-A levels were reported to be related with adverse pregnancy outcomes. We aimed to determine the role of first trimester pregnancy associated plasma protein-A for poor outcomes in preterm isolated oligohydramnios cases.
Material and Methods: Fifty-one patients with singleton pregnancies diagnosed as isolated oligohydramnios at 28/0–36/6 weeks of gestation and 110 gestational age matched healthy controls between January and December 2015 were included. Maternal age, gestational age at delivery, mode of delivery, indication for cesarean section, Apgar scores at first and fifth minutes, birth weight, neonatal intensive care unit admission and mortality were recorded. Pregnancy associated plasma protein-A levels were compared between groups and its role in adverse perinatal outcomes was evaluated.
Results: Pregnancy associated plasma protein-A levels and pregnancy outcomes were similar in two groups ($p > 0.050$) except birth weight, gestational age at delivery and presence of fetal distress. Pregnancy associated plasma protein-A levels did not differ in terms of delivery mode, presence of fetal distress, first and fifth minutes Apgar scores and neonatal intensive care unit admission ($p = 0.323, 0.650, 0.990, 0.112, 0.853$). Also, it was not determined as a risk factor for cesarean section, presence of fetal distress, low Apgar scores and neonatal intensive care unit admission.
Conclusion: Pregnancy associated plasma protein-A, a well-known prognostic factor for some of high risk pregnancy conditions, may not be used as a marker in preterm isolated oligohydramnios cases.

Introduction

Oligohydramnios, which is a common concern for obstetricians, is defined as an amniotic fluid index (AFI) below five centimeter [1,2]. Although the incidence varies depending on the patient selection of studies, gestational age and definition of oligohydramnios, it has been reported to be 0.5–5% [3,4]. However oligohydramnios is usually accompanied with congenital anomalies, hypertension, diabetes, preterm premature rupture of membranes and intrauterine growth restriction (IUGR), it can be an isolated finding with no coexisting medical or obstetric condition [5]. Oligohydramnios is closely related with adverse pregnancy outcomes such as increased fetal distress risk, low Apgar score, postmaturity and meconium aspiration syndrome [6–8]. On the other hand, the implications of isolated oligohydramnios (IO) on pregnancy outcome are still controversial. Recently, there is only a few data in the literature about the management and pregnancy outcomes of IO. Therefore a marker, which can determine the optimum delivery mode and adverse perinatal outcomes for IO cases is crucial.

Pregnancy associated plasma protein-A (PAPP-A) is a glycoprotein, which participates in releasing of insulin like growth factors [9]. It is produced by placenta and desidua [10]. PAPP-A facilitates the breakdown of insulin like growth factor binding protein 4 [11].

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Impairment in releasing of insulin like growth factor increase the tendency for placental insufficiency [12]. Consequently; this may result in adverse pregnancy outcomes.

PAPP-A is a widely used marker for antenatal screening at 11–14th gestational weeks for fetal anomalies such as Down syndrome in combination with maternal age, fetal nuchal translucency and maternal serum human chorionic gonadotropin [13]. Besides this, several studies have investigated the association between PAPP-A and adverse pregnancy outcomes. Low PAPP-A levels were found to be related with increased IUGR, preterm delivery, preeclampsia, abortion, low birth weight and intrauterin fetal death [14–19].

To the best of our knowledge, this is the first study to evaluate the role of PAPP-A for adverse pregnancy outcomes in preterm IO. In the present study, we aimed to determine the role of first trimester PAPP-A for adverse perinatal outcomes such as cesarean section for nonreassuring fetal heart rate, low Apgar score, admission to neonatal intensive care unit (NICU) and perinatal death in pregnancies with preterm IO.

Material and methods

This is a retrospective study conducted in a university affiliated tertiary hospital between January 2015 and December 2015. Singleton pregnancies who were diagnosed as IO at 28/0 and 36/6 weeks of gestation were included. All study participants were evaluated with a sonographic assessment by an experienced radiologist blinded to patients data in order to avoid interobserver variability. AFI was calculated as the sum of the vertical diameters of the deepest pocket in each four quadrants of the gravid uterus. AFI below five centimeter was diagnosed oligohydramnios.

The exclusion criteria of the present study to diagnose IO were as follows; pregnancies complicated by chronic and gestational hypertension or preeclampsia, diabetes, congenital anomalies, IUGR, history of preterm delivery, premature rupture of membranes, suspected chorioamnionitis, any maternal inflammatory or renal diseases and polyhydramnios (AFI > 25 cm) at the initial ultrasonographic and clinical assessment. A total of 71 singleton pregnancies with IO were included. Among those, patients with missing first trimester screening test results were excluded. The data of remaining 51 patients and 110 gestational age matched healthy controls were obtained from electronic health records. Maternal age, gestational age at delivery, mode of delivery, indication for cesarean section, Apgar scores at first and fifth minutes, birth weight, perinatal NICU admission and perinatal mortality were recorded. Adverse perinatal outcomes were defined as Apgar score at first minute <7, at fifth minute <7, cesarean section for nonreassuring fetal heart rate, presence of fetal distress, NICU admission and perinatal death.

The diagnosis of fetal distress has been maintained by the presence of one of the followings: fetal heart rate ≥180/min, slowing of the fetal heart rate after each contraction, persistent slowness of heart rate <120/min, second or third degree meconium stained amniotic fluid.

In the present study, the NICU admission criteria were as follows; neonates with transient problems which requires cardiorespiratory monitoring, necessity for intravenous fluid therapy, jaundice infants requiring closer monitoring and peripheral intravenous fluid therapy, preterm neonates below 32 weeks of gestation, respiratory distress syndrome, neonatal sepsis, exchange transfusion and sustained assisted ventilation. Infants with respiratory distress, tachypnea, nasal flaring, grunting and a grainy shadow, air bronchogram, and white lung in chest x-ray have been diagnosed as RDS. The sepsis has been diagnosed with the presence of at least three of the following: temperature instability, tachypnea

(>70/min), feeding intolerance, abdominal distension, hepatosplenomegaly, dyspnea, lethargy, tachycardia (HR > 190bpmin) and bradycardia (HR < 90bpmin).

In our clinic, as part of first trimester screening test between 11 and 14th weeks of gestation, blood samples for PAPP-A measurement were taken from antecubital vein when the patient is in sitting position, using the vacutainer system. The serum was obtained by centrifugation at 4000 rpm for 15 min. Obtained materials were frozen in −80 °C prior to transport. An immulite immuno-analyser (Siemens Healthcare Diagnostics) was used to measure quantitative PAPP-A level. The results were reported in the clinical genetic laboratory in Istanbul.

This study was approved by the local ethics commitee of our hospital (2011-KAEK-25 2015/24-09).

Statistical analysis

Shapiro Wilk test was used for assessing whether the variables follow normal distribution or not. Variables were reported as mean (minimum: maximum) or median (minimum: maximum) values. According to normality test result, independent samples t test or Mann Whitney U test were used for comparison of groups. Categorical variables were compared by Chi-square test and Fisher's exact test. In order to examine whether the PAPP-A level affects birth type, fetal distress, Apgar first minute <7 and Apgar fifth minute <7 and NICU admission, binary logistic regression analysis was performed. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version21.0. Armonk, NY: IBM Corp.) was used for statistical analysis and a p value of less than 0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of patients were demonstrated in Table 1. There was no significant difference between IO and control group in terms of maternal age, delivery mode, Apgar first and fifth minute scores, NICU admission and PAPP-A levels. Birth weight and gestational age at delivery were significantly lower in IO group, also the number of patients, complicated with fetal distress was significantly higher in IO group

Table 1
Clinical characteristics of study and control groups.

	Isolated oligohydramnios (n = 51)	Control group (n = 110)	p value
Age (years)	27 (20:36)	29 (18:39)	0.123
Gestational age at delivery (week)	34 (32:39)	37 (35:41)	**0.032**
Birth weight (kilogram)	2.93 ± 0.45 (1.75:4.10)	3.32 ± 0.42 (2.27:4.59)	**<0.001**
Delivery mode			0.096
Cesarean section (n,%)	34 (66.70%)	58 (52.70%)	
Normal vaginal delivery (n,%)	17 (33.30%)	52 (47.30%)	
Apgar 1. minutes			
(<7) (n,%)	12 (23.50%)	23 (20.90%)	0.708
Apgar 5. minutes			
(≥7) (n,%)	4 (7.80%)	11 (10%)	0.777
NICU admission (n,%)	15 (29.4%)	24 (21.8%)	0.065
Presence of fetal distress (n,%)	20 (39.2%)	10 (9.1%)	**<0.001**
PAPP-A (mIU/ml)	3.11 ± 2.31	3.41 ± 2.35	0.448

NICU: neonatal intensive care unit, PAPP-A: pregnancy associated plasma protein-A.
*Statistically significant (p ≤ 0.05) values were presented in bold.

($p < 0.001$). There was no maternal and neonatal mortality in both IO and control groups.

When PAPP-A levels of patients were compared, who were complicated with adverse pregnancy outcomes among IO group according to cesarean section rate, presence of fetal distress, Apgar score first minutes <7, Apgar score fifth minutes <7 and requirement of NICU admission, there were no significant difference in each group (p values were respectively 0.323, 0.650, 0.990, 0.112 and 0.853) (Table 2).

In binary logistic regression analysis to evaluate whether PAPP-A level affects delivery mode and presence of fetal distress; PAPP-A levels were not determined as a risk factor (OR = 1.08, 95% CI = 0.84–1.38, $p = 0.562$ and OR = 0.94, 95% CI = 0.73–1.22, $p = 0.644$). Also, PAPP-A was not a risk factor for Apgar first and fifth minutes <7 and necessity of NICU admission (OR = 0.95, 95% CI = 0.70–1.28, $p = 0.713$; OR = 0.99, 95% CI = 0.62–1.56, $p = 0.950$ and OR = 1.03, 95% CI = 0.88–1.20, $p = 0.732$, respectively).

Discussion

The primary finding of the present study is that IO at preterm pregnancy is not associated with adverse pregnancy outcomes except low birth weight, higher rate of fetal distress and preterm delivery. Secondly, there is no difference according to PAPP-A levels between IO and control group. Moreover, PAPP-A does not significantly differ in terms of cesarean section rate, presence of fetal distress, Apgar scores at first and fifth minutes <7, requirement of NICU admission and it can not be determined as a risk factor for adverse pregnancy outcomes.

Oligohydramnios which is commonly encountered by obstetricians in daily clinical practice is generally known to be associated with higher ratios of perinatal mortality and morbidity [6]. Therefore, oligohydramnios gives rise to keep some adverse perinatal outcomes in consideration. On the other hand, the possibility of adverse perinatal outcomes in the presence of oligohydramnios as an isolated finding without any other accompanying medical or obstetric conditions is still under debate [7,8]. In addition to this, the optimal management and obstetric outcomes of IO are also controversial [20,21]. Previous studies have shown that fetal distress risk and cesarean delivery rates were increased in IO group [3,22]. In a meta-analysis of Chauan et al.; IO was found to be associated with increased fetal distress risk and cesarean delivery [7]. Moreover Casey et al. reported that IO was related with the risk for induction of labor, stillbirth, fetal distress, NICU requirement and neonatal death [8]. Contrary to these, other studies claiming IO was not associated with adverse pregnancy outcomes are also

Table 2
PAPP-A levels for adverse perinatal outcomes in preterm isolated oligohydramnios.

	PAPP-A level	*p* value
Delivery mode		0.323
Cesarean section (n = 34)	2.25 (0.38:9.90)	
Normal vaginal delivery (n = 17)	2.97 (0.90:9.34)	
Fetal distress		0.650
Positive	2.26 (0.38:9.90)	
Negative	2.39 (0.90–9.34)	
Apgar 1. minutes		0.990
<7	2.70 (0.38:9.76)	
≥7	2.52 (0.52:9.90)	
Apgar 5. minutes		0.112
<7	3.88 (0.60:9.76)	
≥7	2.46 (0.38:9.90)	
NICU admission		0.853
Positive	2.68 (0.38:9.76)	
Negative	2.57 (0.52:9.90)	

NICU: neonatal intensive care unit.

available [5]. One point that gives rise to think about these conflicting results is gestational age.

At term pregnancies, Ashwal et al. reported similar pregnancy outcomes in IO and control group [3]. Likewise, in the study of Conway et al., in term gestational age matched patients and in control group, neonatal outcomes did not differ [20]. Also, Marina et al. reported in their study that there was no difference in IO group in terms of perinatal outcomes except for an increased risk of small for gestational age infants [6]. In the meta-analysis of Rossi et al. including 679 IO cases, it was found that while obstetrical interventions were more common among IO group, pregnancy outcomes were similar compared to normal amniotic fluid pregnancies [23].

At preterm pregnancies, data regarding the management of IO cases is quite limited. A study that evaluates 65 women with IO between 17 and 37th weeks of gestation, showed that preterm delivery were more common in IO group [24]. Similarly, Melamed et al. reported that pregnancies complicated with IO were more likely to have lower birth weights, higher rates of preterm delivery and cesarean section [25]. Also, Hashimato et al. stated that low-normal amniotic fluid was associated with preterm birth, small for gestational age infant and higher NICU admission rates [26]. Consistent with previous studies, we presented that IO at preterm pregnancies was related with low birth weights and we found an increased risk for development of fetal distress in IO group as compared to controls. Our results may be attributed to iatrogenic prematurity. Hence, PAPP-A, a well-known marker related with adverse pregnancy outcomes, may be valuable in order to clarify the management in pregnancies complicated with IO especially under 37th week of gestation.

While we were searching the literature for the relation of PAPP-A with some of the adverse neonatal and perinatal outcomes, we came across several studies investigating the data about this topic. In previous studies, decreased levels of PAPP-A in early pregnancy was reported to be associated with increased risk of fetal loss, preeclampsia, pregnancy induced hypertension or small for gestational age, preterm birth, stillbirth, preterm premature rupture of membranes and placental abruption [11,27]. This may be explained by lower placental size and decreased placental perfusion, which is most probably related to decreased production of PAPP-A [11,12,14,28]. Among the patients with lower levels of PAPP-A the ones, who were most prone to stillbirth, IUGR and preterm delivery at very early weeks of gestation, were accompanied by small sized placentas and increased alpha fetoprotein levels without disturbed uterine artery doppler velocimetry [29]. In addition to this, Kirkegaard et al. evaluated the neonatal outcomes of 9450 singleton pregnant women who had involved in prenatal screening program. They stated that low PAPP-A levels were significantly associated with NICU admission requirement and neonatal diseases such as hypoglycemia, jaundice and low Apgar scores independently from birth weights and preterm delivery [30]. In another study investigating the risk of intrapartum fetal distress development according to first trimester PAPP-A levels, low PAPP-A levels were reported to increase the risk for intrapartum fetal distress development and consequently the likelihood of cesarean section [31]. Uccella et al. involved 1037 pregnant women which of 152 had low PAPP-A levels in their study. After correction for possible confounders such as hypertension, preterm delivery, small for gestational age and labor induction; umbilical artery pH was significantly lower in low PAPP-A group and also the rates of emergency cesarean delivery for nonreassuring fetal status were higher [32]. In a study analyzing the values of concentration of PAPP-A in pregnancies complicated with preterm delivery, preeclampsia and fetal growth restriction, it was stated that there was statistically significant difference in fetal body weight, Apgar scores at fifth minute and

gestational age at birth according to the PAPP-A levels. They concluded that differences in PAPP-A concentration should be considered to keep in mind that more careful and delicate antepartum surveillance might be required for avoiding adverse perinatal outcomes in that selected group of patients [33].

In the current study, we searched that among patients whose pregnancies were complicated with IO whether there was a difference in PAPP-A levels according to the delivery mode (cesarean or vaginal delivery), presence of fetal distress, Apgar scores (first and fifth minute <7 and ≥7) and requirement of NICU admission. PAPP-A levels did not differ in any of the groups. But, although statistically not significant, PAPP-A levels were lower only in cesarean group and in the patients who developed fetal distress among IO group.

However, before making an accurate conclusion, it should be better to keep in mind that low levels of PAPP-A is poorly sensitive except when its levels are extremely low, which increases its predictivity for adverse neonatal outcomes. In addition to this, most of the patients whose pregnancies were complicated with high risk pregnancy conditions and adverse neonatal outcomes do not have low levels of PAPP-A [16,28].

There are several limitations for the current study. First, this study has a small sample size which arose from single center. Second, it has a retrospective design and therefore potential bias could not be excluded while validating the informations from medical records. Third, PAPP-A levels at 11–14th weeks are analyzed and the relationship between PAPP-A levels at the time of diagnosis of IO and perinatal outcomes are not determined. Finally, PAPP-A values are not divided into percentiles or quartiles and perinatal outcomes are not evaluated according to the percentiles or quartiles.

Conclusion

Isolated oligohydramnios is a condition, which thought to be related with adverse pregnancy outcomes, encountered in daily practice of obstetricians. Although, PAPP-A, a well-known prognostic factor for some of high risk pregnancy conditions, may not be used as a marker in such a highly selected patient group. Further studies with more study populations are required to elucidate this relationship between PAPP-A and presence of adverse perinatal outcomes.

Conflict of interest

The authors declare that they have no conflict of interest relevant to this article. The authors alone are responsible for the content and writing of the paper. The authors have had full control of all primary data and they agree to allow the journal to review their data if requested.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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