Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 72–75

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Association of first-trimester pregnancy-associated plasma protein A levels and idiopathic preterm delivery: A population-based screening study

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ARTICLE INFO

Article history:
Accepted 4 June 2014

Keywords:
Pregnancy-associated plasma protein A (PAPP-A)
Preterm labor
first trimester biomarker

ABSTRACT

Objective: This study aims to determine the strength of relationship between pregnancy-associated plasma protein A (PAPP-A) concentrations, using a Thai-specific reference range, and rates of idiopathic preterm delivery.

Materials and methods: A retrospective cohort study was conducted on consecutive singleton pregnancies, undergoing first-trimester screening for fetal Down syndrome, between January 2007 and July 2012, at our network hospitals in the northern part of Thailand. The prospective database was assessed for the records with complete outcome information, including PAPP-A concentrations, gestational age at delivery, medical and obstetric complications, and fetal and pregnancy outcomes. Pregnancies with potential causes of preterm delivery were excluded. The recruited women were assigned to two groups; a group with normal PAPP-A levels ($\geq 10^{th}$ percentile) and a group with low PAPP-A levels ($<10^{th}$ percentile). The main outcome was the rate of idiopathic preterm births in the two groups.

Results: Of 6867 screened women, 3830 were available for analysis and 670 were excluded because of potential confounders. Of the remaining 3160, 302 had low PAPP-A levels and 2858 had normal PAPP-A levels. The rates of spontaneous preterm births at ≤36 weeks, ≤34 weeks, and ≤32 weeks of gestation were significantly higher in women with low PAPP-A levels (7.6% vs. 17.9%, 3.1% vs. 11.9%, and 2.2% vs. 11.9%, respectively), with a relative risk of 2.37, 3.79, and 5.41 for preterm birth, respectively.

Conclusion: A PAPP-A level of $\leq 10^{th}$ percentile was significantly associated with an increased risk for idiopathic preterm birth. Therefore, pregnant women with low PAPP-A levels in the first trimester should be considered at a high risk of preterm delivery.

Introduction

Preterm birth is the most common direct cause of neonatal death, especially in developing countries. It accounts for 27% of neonatal deaths worldwide, comprising over 1 million deaths annually [1]. All attempts must be made to prevent this serious event. Additionally, the rates of preterm birth are increasing. The rate in our region, the northern part of Thailand, is as high as 15% of live births. In the past, medical efforts focused on ameliorating the consequences of prematurity rather than preventing its occurrence. This approach resulted in improved neonatal outcomes, but it remains costly in terms of the suffering of both infants and their families and the economic burden on society. Currently, primary prevention of preterm birth is increasingly being emphasized. Several strategies have been introduced, such as public education, smoking cessation, or improved nutritional status. Widely accepted strategies in the recent years may include progesterone administration in cases of prior preterm birth, and current singleton pregnancies with short cervical length or cervical cerclage in selected cases [2]. Owing to the availability of effective strategies for prevention of preterm birth, risk identification of preterm birth is even more essential. Identification of risk factors for preterm delivery early in pregnancy may provide an opportunity for

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http://dx.doi.org/10.1016/j.tjog.2015.12.007

intervention to prevent this complication; however, most preterm births occur in case of women with no risk factors, and the number of effective interventions is limited. Since first-trimester serum marker screening for fetal Down syndrome has been used worldwide, it has been shown that an unexplained low levels of pregnancy-associated plasma protein A (PAPP-A), a component of serum markers, is strongly related to preterm delivery and other adverse outcomes of pregnancy [3,4]. First-trimester screening for Down syndrome, PAPP-A, and beta-human chorionic gonadotropin (β-hCG), is routinely offered in our geographical regions. Therefore, it is possible that PAPP-A levels may help identify pregnant women at a higher risk of preterm delivery. As already known, PAPP-A concentrations in maternal serum vary depending on several factors, including maternal size and ethnicity, and each geographical region should have its own reference ranges [5,6]. Moreover, in most previous studies, other predisposing factors of preterm birth were not strictly controlled. Therefore, we conducted this study to determine the strength of relationship between PAPP-A concentrations using our own reference range [5] and rates of idiopathic preterm delivery.

Patients and methods

A retrospective cohort study was conducted on consecutive singleton pregnancies undergoing first-trimester screening for fetal Down syndrome between 11 weeks and 14 weeks of pregnancy, at our 32 network hospitals in the northern part of Thailand. We have established a program for prenatal Down syndrome screening and a prospective database since 2010. All pregnant women attending antenatal care clinics at our network hospitals have routinely been offered first-trimester Down syndrome screening, regardless of maternal age. Baseline demographic data of the women, including maternal age, parity, maternal body weight, ethnic origin, smoking habits or illicit drug use, as well as medical complications were assessed and recorded in the protocol form at the time of blood sample collection. The collected blood samples were immediately transferred to the laboratory and were centrifuged for serum separation. The bioassays for PAPP-A and free β-hCG were performed in batches to eliminate interassay variations, using a DELFIA Xpress system (Perkin Elmer, Waltham, MA, USA). The absolute concentrations of serum PAPP-A, and free β-hCG were converted to multiple of medians (MoM) based on Thai gestation-specific medians and weight correction [5]. A combined risk of 1:250 or greater was considered as positive, and karyotyping would be offered.

The database of our fetal Down syndrome screening program between 2010 and 2012 was assessed for the records that had complete outcome information, including PAPP-A concentrations, gestational age at delivery, medical and obstetric complications, and fetal and pregnancy outcomes. The women were enrolled in our screening program with written informed consent. Inclusion criteria included the following: (1) Thai ethnicity; (2) singleton pregnancies; (3) reliable gestational age based on the last menstrual period and ultrasound examination for crown–rump length in the first trimester, using real-time machines; (4) no history of previous spontaneous preterm birth; and (5) no medical or obstetric complications. Exclusion criteria were as follows: (1) late-occurring pregnancy complications such as preeclampsia, placental abruption, placenta previa, etc.; (2) fetal anomalies; (3) fetal chromosomal abnormalities; (4) incomplete data, loss to follow-up, or unavailability of pregnancy outcomes; and (5) preterm births indicated.

The recruited women were assigned to two groups: one group with normal PAPP-A levels ($\geq 10^{th}$ percentile; equivalent to 0.53 MoM) and the other group with low PAPP-A levels ($<10^{th}$ percentile). The main outcome was the rate of spontaneous preterm births in the two groups. Preterm births were classified into three groups: birth before 37 complete weeks, 34 complete weeks, and 32 complete weeks of gestation. This study was ethically approved by the institute review boards.

Statistical analysis

The statistical analysis was performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). Descriptive statistics were used to compare baseline characteristics between the two groups, using Student *t* tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. A p value of <0.05 was considered statistically significant. Relative risk for preterm birth for pregnancy with a low PAPP-A level was calculated, as well as 95% confident interval. A receiver–operator curve was also constructed to determine the diagnostic performance of low PAPP-A levels in predicting preterm birth.

Results

During the 3 years of study, the database search identified 6867 pregnant women with first-trimester screening in the 34 network hospitals in the northern part of Thailand. However, only 3830 had complete follow-ups with available fetal and pregnancy outcomes. Most cases were excluded at this step because of incomplete data of the neonatal or maternal status, and some with no delivery at the time of analysis. After a thorough review, 670 women were further excluded because of an association with potential confounders for spontaneous or intended preterm delivery, for example, prior preterm birth, preeclampsia, severe fetal growth restriction, placenta previa, placental abruption, smoking, and several medical and other complications, as shown in Table 1. Of 670 excluded women, the prevalence of preeclampsia in the group of low PAPP-A levels was significantly higher, 9.5% versus 3.4%. The remaining 3160 women were available for analysis. The baseline characteristics of pregnant women between the group of normal PAPP-A levels and that of low PAPP-A levels are demonstrated in Table 2. Medians of corrected MoMs of PAPP-A among pregnancy with term birth and preterm birth before 37 complete weeks, 34 complete weeks, and <32 complete weeks of gestation were 1.39, 1.27, 0.97, and 0.80 MoM, respectively. The mean gestational age and mean birth weight were significantly lower in the group of low PAPP-A levels, 38.1 weeks versus 36.3 weeks and 3043 g versus 2713 g, respectively. Notably, maternal weight in the group of normal PAPP-A levels was significantly lower than that in women with low PAPP-A levels, 53.4 kg versus 58.9 kg.

Table 1
Pregnancy-associated complications excluded from the analysis.[a]

	Total ($N = 670$)
Chronic hypertension	76 (2.0%)
Heart disease	19 (0.5%)
Prior preterm birth	120 (3.1%)
Placenta previa	49 (1.3%)
Pregestational DM	89 (2.3%)
Preeclampsia	154 (4.0%)
Smoking/alcohol	11 (0.3%)
Fetal growth restriction	122 (3.2%)
Other complications[b]	89 (2.3%)

DM = diabetes mellitus.
[a] One patient might have more than one complication.
[b] Other medical or obstetric complications with theoretical risk of preterm labor such as placental abruption, thyrotoxicosis, thalassemia disease, etc.