Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 358–361

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

First trimester maternal serum analytes and second trimester uterine artery Doppler in the prediction of preeclampsia and fetal growth restriction

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ARTICLE INFO

Article history:
Accepted 4 January 2017

Keywords:
PAPP-A
ADAM12
UAD
Preeclampsia
Fetal growth restriction

ABSTRACT

Objective: This study aimed to determine whether pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotropin (β-hCG), a disintegrin and metalloprotease 12 (ADAM12), and placenta protein 13 (PP13) in the first trimester, and uterine artery Doppler (UAD) in the second trimester, predict preeclampsia and fetal growth restriction (FGR).

Materials and methods: Maternal serum levels of PAPP-A, free β-hCG, ADAM12, and PP13 at $11–13^{+6}$ weeks of gestation and bilateral uterine artery pulsatility index (PI) at 22–24 weeks of gestation were measured in a nested case–control study within a prospective cohort. The serum analytes and Doppler measurements were compared for uncomplicated pregnancies and pregnancies complicated by preeclampsia and FGR. The efficacy of biochemical and Doppler measurements for the prediction of preeclampsia and FGR was investigated.

Results: Compared with gestational age-matched controls (n = 200), the mean PAPP-A and ADAM12 were lower ($P < 0.001$, $P < 0.05$) in pregnancies complicated by preeclampsia (n = 462) and FGR (n = 350). The median uterine artery mean PI was higher ($P < 0.001$) in preeclampsia and FGR groups. However, the median free β-hCG and PP13 were not significantly different from normal ($P > 0.05$). In screening for preeclampsia and FGR, assuming a fixed false positive rate (FPR) of 10%, the detection rates were 72% and 68% for a combination of PAPP-A, ADAM12, and UAD, respectively.

Conclusion: First trimester PAPP-A and ADAM12 levels and second trimester uterine artery PI are associated with adverse pregnancy outcomes. The combination of biochemical markers and UAD improves the screening efficiency for the prediction of preeclampsia and FGR.

Introduction

Preeclampsia and fetal growth restriction (FGR) are contributors to perinatal mortality and morbidity, as well as the long-term cardiovascular health of the mother and child. Modern antenatal care provision is focused on early identification of risks, thereby allowing early commencement of management strategies to minimize the risk of adverse pregnancy outcomes [1]. The concentration of maternal serum analytes in the first trimester reflects trophoblast secretory activity. Several biochemical markers have been evaluated for the ability to predict preeclampsia and FGR in the first trimester, prior to onset of clinical signs. However, the accuracy of these markers is suboptimal for clinical use. Prior studies have shown an association between low maternal serum pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (β-hCG) in the first trimester and the subsequent development of adverse pregnancy outcomes such as preeclampsia or FGR. However, the predictive efficiency of PAPP-A for adverse pregnancy outcomes was modest [2–4]. Additional studies have focused on some novel serum analytes, such as a disintegrin and metalloprotease 12 (ADAM12) and placenta protein 13 (PP13), which show promise in screening for suboptimal outcomes [5–7]. However, some findings have been inconsistent. Abnormal uterine artery Doppler pulsatility index (PI) assessment in the second trimester might also correlate with suboptimal outcomes, but its role in prediction of later pregnancy complications is controversial [8–10].

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http://dx.doi.org/10.1016/j.tjog.2017.01.009

The objective of our study was to examine the possible association between abnormal serum biochemical markers (PAPP-A, free β-hCG, ADAM12, and PP13) at 11–13^{+6} weeks of gestation, alone or in combination with abnormal uterine artery PI at 22–24 weeks of gestation, and adverse pregnancy outcomes. An additional objective was to investigate the accuracy of first trimester serum analytes and second trimester uterine artery Doppler (UAD), both individually and in combination, in the prediction of FGR and preeclampsia.

Materials and methods

General data

This was a nested case–control study of a prospective cohort. Patients with singleton pregnancies who presented to Tianjin Central Hospital of Gynaecology and Obstetrics, Tianjin, China from 2013 to 2015 for first trimester aneuploidy screening at 11–13^{+6} weeks of gestation were eligible for inclusion, and aneuploidy or major congenital malformation was excluded. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Tianjin Central Hospital of Gynaecology and Obstetrics. Written informed consent was obtained from all participants and was followed from the first-trimester to delivery with recorded pregnancy outcomes.

Maternal serum analytes

Serum PAPP-A and free β-hCG were measured as a part of routine first trimester aneuploidy screening using an immunofluorometric analysis. With maternal consent, serum was collected and stored at −80 °C. A maternal serum sample of 25 μl was used to determine ADAM12 and PP13 concentrations through a time-resolved fluorescent immunoassay, where both of the concentrations were directly proportional to the fluorescence measured at 615 nm. Concentrations of serum analyte were expressed as multiples-of-median (MoM), adjusted for gestational age. All samples with subsequent development of FGR or preeclampsia were measured and compared with gestational age-matched controls without any adverse pregnancy outcome during the same period.

Sonographic evaluation

A routine ultrasound examination was performed at 22–24 weeks of gestation for detection of fetal growth and defects. Patients enrolled also underwent bilateral UAD assessment. This examination was performed using transabdominal ultrasound with color-flow mapping. Each uterine artery was identified and the PI was measured and averaged using at least 3 good quality and similar consecutive waveforms. The presence or absence of early diastolic notches on each side of the uterine artery was noted. These data were also adjusted for gestational age and converted into MoM.

Clinical diagnoses

Preeclampsia was defined according to the guidelines of the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy, based on systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on 2 recordings at least 4 h apart, with the presence of proteinuria ≥300 mg in 24 h or ≥1+ protein on dipstick analysis, after 20 weeks of gestation in a woman with previously normal blood pressure [11]. FGR was defined as birth weight below the fifth percentile for gestational age [12].

Statistical analysis

Serum analytes and uterine artery PI were expressed as MoM and comparisons were performed by t-test between 2 groups (preeclampsia and normal pregnancies, FGR and normal pregnancies). The detection rates of preeclampsia and FGR were calculated using serum analytes and uterine artery PI, both individually and in combination. Receiver-operating characteristic curves (ROC) were constructed, and the area under the curve (AUC) was compared in the 2 models using non-parametric U statistics, with a false positive rate (FPR) calculated for each model. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 19.0.

Results

Subject demographics

Of 5000 singleton nulliparous pregnancies enrolled, 112 were lost to follow-up and 29 underwent spontaneous abortion; 4859 patients with complete outcome information were available for analysis. Of these, 462 (9.5%) developed preeclampsia (25% also had FGR) and 350 (7.2%) developed FGR without preeclampsia, compared with gestational age-matched controls with normal outcomes (n = 200). The study population underwent measurement of PAPP-A, free β-hCG, ADAM12, and PP13 at 11–13^{+6} (median 12) weeks of gestation, and uterine artery PI measurement at 22–24 (median 23) weeks. The median maternal age was not significantly different among the 3 groups ($P = 0.452$). Compared to controls, patients who subsequently developed preeclampsia were more likely to have a higher pre-pregnancy body mass index ($P = 0.033$) (Table 1).

Association of serum analytes and UAD with pregnancy outcome

The results comparing first trimester serum analytes and UAD PI in the control group and cases with preeclampsia and FGR are shown in Table 2. Patients who developed preeclampsia had significantly lower PAPP-A MoM (0.79 vs. 1.19, $P < 0.001$) and ADAM12 MoM (0.86 vs. 1.19, $P = 0.043$) compared to controls. In the FGR groups, the median PAPP-A and ADAM12 were also significantly lower (0.83 vs. 1.12, $P < 0.001$ and 0.90 vs. 1.12, $P = 0.036$, respectively). Moreover, the UAD PI levels in preeclampsia and FGR patients were significantly higher than normal (1.52 vs. 1.02 and 1.39 vs. 1.02, $P < 0.001$ in both cases). However, there were no significant differences in free β-hCG MoM in both preeclampsia and FGR groups, compared to controls (0.92 vs. 1.00, $P = 0.536$ and 0.94 vs. 1.00, $P = 0.727$). In patients with preeclampsia or FGR, the median PP13 MoM values were not significantly different from normal (1.12 vs. 1.10, $P = 0.798$ and 1.05 vs. 1.10, $P = 0.621$).

Table 1
Baseline maternal characteristics.[a]

	Preeclampsia (n = 462)	FGR (n = 350)	Control (n = 200)	P-value
Maternal age (years)	30.2 ± 4.6	29.4 ± 1.9	28.6 ± 2.3	0.452
Time of measurement of biomarker (weeks)	12.6 ± 1.2	11.9 ± 2.2	12.0 ± 1.8	0.320
Time of measurement of UAD PI(weeks)	23.0 ± 5.6	22.6 ± 7.0	23.5 ± 4.4	0.562
Body mass index (kg/m^2)	33.6 ± 9.2	29.2 ± 8.0	28.2 ± 6.9	0.033

[a] Data expressed as mean ± standard deviation.

Table 2
Comparison of biomarker levels and UAD PI among study groups.[a]

	Preeclampsia (n = 462)	FGR (n = 350)	Control (n = 200)	P-value	
				Preeclampsia	FGR
PAPP-A MoM	0.79 (0.71–0.91)	0.83 (0.67–1.00)	1.19 (0.88–1.50)	<0.001	<0.001
ADAM12 MoM	0.86 (0.73–1.01)	0.90 (0.68–1.12)	1.12 (0.82–1.45)	0.043	0.036
Free β-hCG MoM	0.92 (0.83–1.03)	0.94 (0.80–1.16)	1.00 (0.85–1.18)	0.536	0.727
PP13 MoM	1.12 (0.89–1.34)	1.05 (0.92–1.21)	1.10 (0.80–1.50)	0.798	0.621
UAD PI MoM	1.52 (0.98–2.10)	1.39 (0.92–1.90)	1.02 (0.63–1.43)	<0.001	<0.001

[a] Data expressed as medians and interquartile ranges.

Sensitivity analysis

We performed sensitivity analysis to determine whether combining ADAM12, PAPP-A, and UAD could improve predictive efficiency for the development of preeclampsia or FGR. The detection rates for preeclampsia were examined using different models. The AUC of PAPP-A was 0.63 and the sensitivity was 26% at 10% FPR; the respective values for ADAM12 were 0.54 and 17%, and those for UAD PI were 0.76 and 52%. The overall predictive efficiency for preeclampsia achieved by combining PAPP-A, ADAM12, and UAD PI was improved, compared with use of either marker alone, with an AUC of 0.89 and sensitivity of 72% at 10% FPR. The detection rates for FGR were also improved, with an AUC of 0.80 and sensitivity of 68% at 10% FPR (Table 3).

Discussion

A growing number of studies have focused on a combination of serum parameters, such as preeclampsia and FGR [13], as screening tests for adverse pregnancy outcomes in the first trimester. This study evaluated the association of combined abnormal first trimester serum analyte values and second trimester UAD with abnormal pregnancy outcomes.

Previous studies indicated that low serum PAPP-A concentrations at $11–13^{+6}$ weeks of gestation are associated with subsequent development of preeclampsia, small for gestational age infants, and spontaneous preterm delivery [14,15]. Recently, several studies suggested that an underlying mechanism by which PAPP-A might affect placental function is through its effect on insulin-like growth factors (IGFs). PAPP-A is a protease for IGF-binding protein (IGFBP), and can inhibit the action of IGFs [16]. Low levels of PAPP-A increase the amount of IGFs in the bound state that are unavailable to promote fetal and placental growth and development [17,18]. This finding is the most plausible mechanism for the decreased PAPP-A levels.

ADAM12 is a placenta-derived multidomain glycoprotein that is thought to be involved in controlling fetal and placental growth and development. Consistent with our results, there is some evidence that in those destined to develop preeclampsia or FGR, the concentration of maternal serum ADAM12 in the first trimester of pregnancy is reduced [5,6]. Similar to PAPP-A, ADAM12 is a protease for IGFBP. Low levels of this analyte reflect an increased amount of IGFs in the bound state that are then unavailable to promote placental development [18].

Although many studies have reached positive conclusions, the results are not consistent. Further investigation with expanded sample sizes is required to support the premise that complications later in pregnancy can be identified by abnormal serum analytes in the first trimester.

The luminal diameter of spiral arteries is increased significantly, and the vascular smooth muscle is replaced by trophoblast cells in normal pregnancy. However, in preeclampsia, a disease of circulatory maladaptation, this process is deficient in trophoblastic invasion and increased resistance in the uteroplacental circulation [19]. In a prospective study involving 8366 singleton pregnancies, Poon et al. [20,21] reported that in women who subsequently developed preeclampsia, the lowest, mean, and highest uterine artery PI were significantly higher than in a control group. The detection rate for early preeclampsia improved to 83.8% using first trimester uterine artery Doppler. Our study demonstrated significant differences in second trimester uterine artery PI measurements between those with preeclampsia or FGR and controls. The association between increased uterine artery PI and subsequent development of preeclampsia or FGR is due to the impaired trophoblastic invasion of the uterine spiral arteries [19]. However, other authors have found no significant differences in uterine artery PI measurements between preeclampsia and control patients, and no effect on screening sensitivity for the prediction of preeclampsia [22–24]. Given that maximal trophoblast invasion occurs during the first trimester, enhanced vascular resistance in the maternal uterine arteries would be detectable at an early stage of pregnancy with impaired placentation [25].

Differences between these studies may be due to the varying criteria used for abnormal uterine artery Doppler PI. We measured the left and right uterine artery PI and the lowest value was analyzed. Alternatively, some studies used the average PI values for both uterine arteries. We expected to observe more consistent results for the relationship between UAD and preeclampsia, regardless of the criteria used to define an abnormal PI value.

In this cohort of 4859 women, data for 462 women with preeclampsia and 350 with FGR were used to devise a predictive model for preeclampsia and FGR that incorporated first trimester serum PAPP-A and ADAM12 and second trimester PI. Second trimester uterine artery Doppler improved the detection rate for preeclampsia to 72% and 68% for FGR at a 10% false positive rate, when combined with first trimester serum analytes.

Table 3
Predictive efficiency of biomarker levels and UAD PI for preeclampsia and FGR.[a]

	Preeclampsia (n = 462)		FGR (n = 350)	
	AUC (95% CI)	Sensitivity 10% FPR	AUC (95% CI)	Sensitivity 10% FPR
PAPP-A alone	0.63 (0.56–0.71)	26%	0.57 (0.52–0.62)	21%
ADAM12 alone	0.54 (0.49–0.58)	17%	0.49 (0.40–0.59)	14%
UAD PI alone	0.76 (0.62–0.90)	52%	0.78 (0.69–0.86)	54%
PAPP-A + ADAM12 + UAD PI	0.89 (0.81–0.99)	72%	0.80 (0.73–0.87)	68%

[a] Data expressed as medians and interquartile ranges.

Conclusion

Our study demonstrates that serum PAPP-A and ADAM12 levels in the first trimester are significantly reduced in patients who develop preeclampsia or FGR. The predictive efficiency of these first trimester serum markers in combination with second trimester

UAD is superior to that achieved by either marker alone. Further investigation of novel biomarkers and ultrasound markers with high predictive value and prognostic information should be translated into clinical practice.

Conflict of interest

All authors have no conflict of interest regarding this paper.

Acknowledgement

This study was supported by a grant from the Science and Technology Fund of Tianjin Municipal Health Bureau (2015KZ079).

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