Original Paper

Fetal Diagnosis and Therapy

Fetal Diagn Ther 2009;25:336–339
DOI: 10.1159/000235880

Received: May 12, 2009
Accepted after revision: June 9, 2009
Published online: September 22, 2009

First-Trimester Uterine Artery Doppler and Serum Pregnancy-Associated Plasma Protein-A in Preeclampsia and Chromosomal Defects

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Key Words
PAPP-A · Uterine artery Doppler · First-trimester screening · Trisomy 21 · Preeclampsia

Abstract
Objective: We examined the potential value of the uterine artery pulsatility index (PI) in pregnancies with fetal aneuploidies and in those that developed preeclampsia (PE) with the aim of distinguishing between these complications in pregnancies with low pregnancy-associated plasma protein-A (PAPP-A). ***Methods:*** Uterine artery PI and serum PAPP-A at 11–13 weeks were measured in 165 cases of PE, including 33 that required delivery before 34 weeks (early PE) and 132 with late PE, and in 301 cases with aneuploidies, including 200 with trisomy 21. Each case of aneuploidy and PE was matched with 4 unaffected controls. ***Results:*** Serum PAPP-A was lower in early PE (0.58 multiples of the normal median, MoM) and in trisomy 21 (0.54 MoM), trisomy 18 (0.22 MoM) and Turner syndrome (0.51 MoM) – but not in late PE (0.90 MoM) – than in controls (1.01 MoM). Uterine artery PI was higher in early PE (1.52 MoM), late PE (1.20 MoM), trisomy 18 (1.20 MoM) and Turner syndrome (1.29 MoM) – but not in trisomy 21 (1.02 MoM) – than in controls (1.0 MoM). ***Conclusion:*** The uterine artery PI at 11–13 weeks may be useful in distinguishing between low PAPP-A due to trisomy 21 and early PE.

Introduction

First-trimester screening for chromosomal abnormalities involves the combination of serum pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (β-hCG) with maternal age and fetal nuchal translucency (NT) thickness [1]. However, low serum PAPP-A is associated with increased risk of both fetal chromosomal abnormalities and with subsequent development of preeclampsia (PE) [2, 3]. Consequently, euploid pregnancies at risk of PE may be mistakenly classified as being at increased risk of chromosomal defects and may be subjected to unnecessary invasive testing by chorionic villous sampling or amniocentesis. One possible way of distinguishing between chromosomal defects and PE is the measurement of the uterine artery pulsatility index (PI), which is reported to be normal in the former and increased in the latter [4–6].

In this study we compare maternal age, fetal NT, serum PAPP-A and free β-hCG, and the uterine artery PI in pregnancies with fetal chromosomal abnormalities and those that develop PE with the aim of distinguishing between these complications in pregnancies with low PAPP-A.

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1015–3837/09/0253–0336$26.00/0

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Table 1. Median (interquartile range) maternal age, crown-to-rump length, NT, PAPP-A MoM, free β-hCG MoM, and uterine artery PI MoM in the different outcome groups

	n	Maternal age years	Crown-to-rump length mm	NT mm	PAPP-A MoM	Free β-hCG MoM	Uterine artery PI MoM
Controls	1,864	32.2 (27.9–35.8)	63.4 (58.6–68.3)	1.7 (1.5–2.0)	1.01 (0.72–1.42)	0.97 (0.66–1.47)	1.00 (0.83–1.22)
Late PE	132	32.4 (27.6–36.7)	62.3 (58.3–69.0)	1.7 (1.5–1.9)	0.90 (0.56–1.24)	0.98 (0.65–1.50)	1.20 (0.95–1.46)*
Early PE	33	31.6 (25.5–35.6)	64.4 (58.0–72.8)	1.7 (1.4–1.9)	0.58 (0.39–1.01)*	1.12 (0.72–1.95)	1.52 (1.30–1.67)*
Trisomy 21	200	38.9 (36.2–41.1)*	64.6 (58.9–70.0)	3.5 (2.7–4.9)*	0.54 (0.38–0.82)*	2.29 (1.47–3.34)*	1.02 (0.81–1.26)
Trisomy 18	55	38.1 (35.4–40.4)*	57.9 (52.8–62.0)*	5.4 (2.5–7.7)*	0.22 (0.13–0.37)*	0.27 (0.14–0.41)*	1.20 (0.96–1.35)*
Trisomy 13	19	38.2 (35.9–41.0)*	58.0 (55.6–64.4)	4.6 (2.3–5.8)*	0.32 (0.22–0.47)*	0.55 (0.39–0.91)	1.24 (1.04–1.33)
Turner	19	33.3 (29.7–35.0)	59.7 (55.6–65.0)	9.3 (7.9–11.6)*	0.51 (0.26–0.88)*	1.19 (0.71–1.92)	1.29 (1.07–1.59)*
Triploidy	8	31.5 (28.8–34.5)	52.1 (49.0–64.9)	1.4 (1.2–1.8)	0.08 (0.04–0.14)*	0.18 (0.08–0.43)*	1.20 (1.02–1.40)

Comparison of each of the outcome groups with the controls by Kruskal-Wallis test with Dunn's procedure.
* $p < 0.0018$.

Patients and Methods

Study Population

In our hospital all pregnant women are offered combined screening for trisomy 21 at 11–13 weeks of gestation. An ultrasound scan is carried out: (1) to confirm the gestational age by measurement of the fetal crown-to-rump length; (2) to diagnose any major fetal abnormalities, and (3) to measure the fetal NT thickness. In addition, the maternal serum PAPP-A and free β-hCG are determined and the results combined with maternal age and fetal NT to calculate the patient-specific risk of trisomy 21 [7, 8]. In this hospital visit we also perform transabdominal color Doppler measurement of the left and right uterine artery PI and record the mean PI as part of a research program on screening for PE [9]. The results of the Doppler studies are not given to the women or their doctors and do not influence the subsequent management of the pregnancies. In addition to the women booking for delivery in our hospital, we see women referred from other hospitals for chorionic villous sampling because routine screening had identified their pregnancies as being at high risk of chromosomal abnormalities. In these women we also perform uterine artery Doppler before chorionic villous sampling. Written informed consent is obtained from the women agreeing to participate in the study for hypertensive disorders, which has been approved by the King's College Hospital Ethics Committee.

This was a nested case-control study. During a 22-month period (between March 2006 and January 2008), we performed first-trimester assessments in 12,489 singleton pregnancies and entered their findings into a computer database. Data on pregnancy outcome were collected from cytogenetic laboratories, hospital maternity records or general medical practitioners. We searched the database and identified 165 pregnancies that subsequently developed PE, including 33 that required delivery before 34 weeks (early PE) and 132 with late PE, 200 cases of trisomy 21, 55 of trisomy 18, 19 of trisomy 13, 19 of Turner syndrome and 8 of triploidy. Each case of aneuploidy and each case of PE was matched with 4 unaffected controls examined on the same day. The controls were pregnancies that did not develop hypertensive complications and resulted in the birth of phenotypically normal babies.

Outcome Measures

The diagnosis of chromosomal abnormalities was made by chorionic villous sampling and cytogenetic analysis. The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [10]. In gestational hypertension the diastolic blood pressure should be ≥90 mm Hg on at least 2 occasions 4 h apart, developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria. In PE there should be gestational hypertension with proteinuria of ≥300 mg in 24 h or 2 readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available.

Statistical Analysis

The measured uterine artery PI, PAPP-A and free β-hCG were converted into multiples of the normal median (MoM) after adjustment for gestation and maternal characteristics as previously described [9, 11]. Comparison between outcome groups was done by the Kruskal-Wallis test with Dunn's procedure.

The statistical software package SPSS 12.0 (SPSS Inc., Chicago, Ill., USA) and XLSTAT version 2008.7.01 (XLSTAT; Addinsoft SARL, New York, N.Y., USA) were used for all data analyses.

Results

Maternal age, fetal NT and crown-to-rump length, serum free β-hCG and PAPP-A, and the uterine artery PI in the outcome groups are compared in table 1. In the PE groups there were no significant differences when compared to the controls in maternal age, fetal NT and crown-

to-rump length, or serum free β-hCG. The uterine artery PI was increased in both early PE and late PE, but more so in the former, and PAPP-A was reduced only in early PE. Trisomy 21 was associated with increased maternal age, fetal NT and serum free β-hCG, but low PAPP-A and a normal uterine artery PI. In trisomies 18 and 13 there was a significant increase in maternal age, fetal NT and uterine artery PI, and a decrease in serum free β-HCG and PAPP-A. Turner syndrome was associated with increased fetal NT and uterine artery PI, decreased serum PAPP-A and normal maternal age and serum free β-hCG. In triploidy maternal age and fetal NT were normal, serum free β-hCG and PAPP-A were very low and the uterine artery PI was increased but, presumably, because of the small number of cases, the increase was not significant.

Discussion

The findings of this study on the pattern of maternal age, fetal NT and serum free β-hCG and PAPP-A in different chromosomal abnormalities are compatible with previous reports [7, 8, 11–13]. Thus, PAPP-A is decreased in all the chromosomal abnormalities examined, the incidence of trisomies but not Turner syndrome and triploidy increases with maternal age, fetal NT is increased in all trisomies and Turner syndrome but not in triploidy, and serum free β-hCG is increased in trisomy 21, decreased in trisomies 18 and 13 and triploidy but is not altered in Turner syndrome.

Low serum PAPP-A at 11–13 weeks is also observed in euploid pregnancies that subsequently develop early PE but, in contrast to chromosomal abnormalities, in early PE maternal age, fetal NT and serum free β-hCG are not significantly different from controls. Another distinguishing factor between early PE and trisomy 21 was the uterine artery PI, which was increased in the former and was normal in the latter. In late PE and the chromosomal abnormalities other than trisomy 21, there was a mild and similar increase in the uterine artery PI. The rate of fetal death between 12 weeks of gestation and term is about 20% for trisomy 21, 80–90% for trisomy 18, trisomy 13 and Turner syndrome, and 100% for triploidy. The finding that, unlike trisomy 21, in the other chromosomal abnormalities the uterine artery PI was increased to about 1.2 MoM, which is the level observed in euploid pregnancies developing late PE, suggests that in these abnormalities there is an element of impaired placentation, which may contribute to their high intrauterine lethality. In terms of the possible predisposition of these chromosomally abnormal pregnancies to PE, the data are limited presumably because the number of affected pregnancies reaching the third trimester is very small. Nevertheless, a few case reports and small series suggested that, certainly in the case of trisomy 13, there is a strong association with PE [14–16]. However, in pregnancies with trisomy 21 the uterine artery PI is similar to the normal unaffected pregnancies, which closely relates to the normal placentation and the low risk of PE which has been demonstrated in these pregnancies [17].

In euploid pregnancies that develop early PE, the low serum PAPP-A may be the mere consequence of the impaired trophoblastic invasion of the maternal spiral arteries and of the secondary decrease in placental function [18]. In contrast, in the pregnancies that developed late PE or were affected by the highly lethal chromosomal abnormalities, although the mean uterine artery PI was similar, there were major differences in serum PAPP-A, which are likely to be the consequence of genetically determined differences in the preproduction and/or secretion of this placental protein [19]. The same is also true of trisomy 21 where serum PAPP-A is about 0.5 MoM and the uterine artery PI is 1.0 MoM.

The main value of our study is in summarizing the similarities and differences at 11–13 weeks between pregnancies developing PE and those complicated by a variety of chromosomal abnormalities. A clinical implication of these findings is in the management of pregnancies presenting with low serum PAPP-A. In such cases the managing physician should examine all additional findings to assess whether the pregnancy is indeed at increased risk of chromosomal abnormalities and in need of chorionic villous sampling, or whether it is more likely that the pregnancy is at increased risk of PE and in need of close monitoring of fetal growth and maternal blood pressure rather than chorionic villous sampling.

A very low level of PAPP-A of 0.1 MoM or less should raise the possibility of dygynic triploidy, in which case serum free β-hCG is invariably also very low. Serum PAPP-A of about 0.3 MoM should raise the possibility of trisomies 18 and 13, in which case serum free β-hCG is also reduced and fetal NT is increased. These chromosomal abnormalities are commonly associated with additional defects, such as holoprosencephaly, exomphalos, megacystis, cardiac and digital defects, which could be easily detectable even in the first trimester of pregnancy especially when the sonographer has been alerted by the biochemical findings [1]. Serum PAPP-A of about 0.5 MoM could be the consequence of trisomy 21, Turner

syndrome or early PE. As highlighted by our findings, in trisomy 21 fetal NT and free β-hCG are increased but the uterine artery PI is normal, whereas in Turner syndrome NT is substantially increased but free β-hCG and the uterine artery PI are normal, and in early PE the uterine artery PI is increased but fetal NT and free β-hCG are normal.

At 11–13 weeks, in a developed country where the average maternal age is about 32 years, the prevalence of trisomies 21, 18 and 13, Turner syndrome and triploidy is 1:500, 1:1,500, 1:4,000, 1:1,500 and 1:2,000, respectively [20, 21]. Therefore, in a screened population of 1,000 pregnancies there would be 2 cases of trisomy 21 and another 2 with other major chromosomal abnormalities. First-trimester combined screening for trisomy 21 identifies about 90% of fetuses with all major chromosomal abnormalities at a false positive rate of 5% or 50 in 1,000. Since the prevalence of early PE is about 0.5% or 5 in 1,000 and an increased uterine artery PI at 11–13 weeks is observed in about 60% of these [3], incorporation of the uterine artery PI in first-trimester screening for trisomy 21 may have only a minor impact on the performance of screening by reducing the false positive rate. However, as explained in the previous paragraph, the assessment of the individual components of screening by means of inclusion of the uterine artery PI is likely to improve the patient-specific management of pregnancies with low PAPP-A. The development of specific algorithms incorporating the uterine artery PI would necessitate large population-based screening studies which are underway.

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